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Nothnagel's Practice

DISEASES

OF THE BLOOD

BY

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PREFACE.

THE excellence of the series of monographs issued under the editorship of Professor Nothnagel has been recognized by all who are sufficiently familiar with German to read these works, and the series has found a not inconsiderable proportion of its distribution in this and other English-speaking countries. I have so often heard regret expressed by those whose lack of familiarity with German kept these works beyond their reach, that I was glad of the opportunity to assist in the bringing out of an English edition. It was especially gratifying to find that the prominent specialists who were invited to co-operate by editing separate volumes were as interested as myself in the matter of publication of an English edition. These editors have been requested to make such additions to the original articles as seem necessary to them to bring the articles fully up to date and at the same time to adapt them thoroughly to the American or English reader. The names of the editors alone suffice to assure the profession that in the additions there will be preserved the same high standard of excellence that has been so conspicuous a feature in the original German articles.

In all cases the German author has been consulted with regard to the publication of this edition of his work, and has given specific consent. In one case only it was unfortunately necessary to substitute for the translation of the German article an entirely new one by an American author, on account of a previous arrangement of the German author to issue a translation of his article separately from this series. With this exception the Nothnagel series will be presented intact.

ALFRED STENGEL.

EDITOR'S PREFACE.

THE articles comprising this volume are authoritative presentations of the more important scientific aspects of Hematology and do not pretend to fill the place of text-books of Clinical Hematology. Details regarding methods of examination have been omitted by the authors of the original articles, and the editor has considered it proper to add only such recent methods as had a bearing on the subjects discussed in the original text. In the same spirit additions to the scientific discussions have been limited to such as might amplify the original articles or present the more recent views of other authors, including those who have not accepted the teachings of the authors of the volume. The task of editing has been made more difficult by the editor's feeling that the character of the volume should not be altered through an attempt to include a wider range of subjects than the original articles contained. The teachings of Ehrlich and his pupils have occasioned not a little controversy; it has seemed proper to refer to the views of some of the opponents. Less occasion was found to add to the article on Chlorosis, for the reason that there has been less activity in the study of this disease, and the knowledge of the present day is more fixed and probably more certain.

ALFRED STENGEL.

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ANEMIA

BY

PROF. DR. P. EHRLICH AND DR. A. LAZARUS

HISTOLOGY OF THE BLOOD, NORMAL AND PATHOLOGIC.

INTRODUCTION.

DEFINITION.—CLINICAL METHODS OF EXAMINATION OF THE BLOOD.

A SOMEWHAT different significance has been given to the word "anemia" in practical medicine and in scientific investigation. The former regards as significant certain striking external symptoms, as pallor of the skin, and a diminished redness of the mucous membrane of the eyes, of the lips, of the buccal cavity, and of the throat. Moreover, these symptoms characterize not only the presence of anemia, but, in accordance with their greater or less intensity, also the degree of the anemia.

It is evident *a priori* that a definition constructed on such a frequent and elementary syndrome must include conditions not belonging together, and omit others which should be included. As a matter of fact, a series of ambiguities and contradictions are referable to this circumstance.

The first problem in a scientific consideration of anemia is to determine carefully the limitation of the term. For this the external symptoms are little adapted, though in their proper place their practical significance is not small.

Etymologically the word anemia signifies an amount of blood less than that in health. This abnormality may be "general," throughout the entire organism; or "local"—that is, confined to a circumscribed region, for instance, a single organ. The latter, the local anemias, will be omitted entirely from consideration.

The amount of blood may be less than normal quantitatively and qualitatively. There may be a diminution of the amount without alteration of the composition, *oligemia;* or there may be a diminution of the essential constituents of the blood independently of general quantity. In this latter case two chief types are differentiated: a

diminution of the hemoglobin, *oligochromemia,* and a diminution of the number of red blood-corpuscles, *oligocythemia.*

The term anemia includes all conditions in which a decrease of the hemoglobin is perceptible. In the great majority of these, but not constantly, there is at the same time more or less oligemia and oligocythemia.

The most important methods of clinical hematology are directed toward the demonstration of these changes.

Quantity of Blood.—The estimation of the entire quantity of blood can not be accomplished by any method now at our disposal. Something can be gathered from observation of the previously mentioned symptoms, namely, the redness or pallor of the skin and mucous membranes; yet these are to a great extent dependent on the composition of the blood (quality of the blood), and not on the turgescence of the peripheral vessels. If the latter is to be taken as a criterion for the entire amount of blood, it is advisable to observe isolated vessels visible to the naked eye, for instance, on the sclera, or even more particularly those on the posterior eye-ground, by means of the ophthalmoscope. Raehlmann has shown that in 60 per cent. of cases of chronic anemia in which the skin and mucous membranes are very pale there is a hyperemia of the retina, a proof that in such cases blood that is paler than normal but not necessarily less in quantity circulates in the vessels. A more important criterion, though valuable only on considerable diminution of the blood, is the quality of the pulse, which is always especially small and soft in marked oligemia.

The flow of blood from punctures gives a further indication of the amount of blood, though an uncertain one, because of the variable coagulability of the blood. Any one who has made frequent blood examinations in anemics must have noticed the extraordinary differences which are manifested. In some cases a drop of blood can scarcely be obtained by the ordinary methods, while in others the blood gushes freely. It is impossible to err in the first instance in inferring an absolute diminution in the amount of blood. Still the turgescence of the peripheral vessels is of only relative value since the blood content of the different organs may be very different.

The problem of estimating exactly the amount of blood has always been recognized as important, and its solution will mark an important advance in hematology. Several clinical methods have been proposed. Tarchanoff suggested that the amount of blood be estimated by comparison of the number of red blood-corpuscles before and after an active artificial sweat, the loss of water in which has been measured.

Omitting many theoretic considerations, this method is much too complicated for practical use.

Quincke proposed a method by means of the transfusion of blood. He claimed that from the number of red blood-corpuscles in the subject before and after the injection of a definite amount of blood containing a known number of red blood-corpuscles, the quantity of blood might readily be estimated. This method also is practicable only in selected cases, and to it there are many theoretic objections. In the first place, it is naturally dependent on the relative number of red blood-corpuscles in the blood, inasmuch as, for instance, the transfusion of normal blood into normal blood would produce no change in the number. This circumstance alone shows that the procedure is practicable in only a few special cases. True, it has been proved that normal blood injected into an individual showing a very small corpuscular count has produced an increase of red blood-corpuscles per cubic millimeter; yet it is extremely hazardous to estimate from this the volume of the preexistent blood, since currents making for circulatory equilibrium and changes in the distribution of the blood undoubtedly follow the transfusion.

It is much more practicable to introduce directly into the circulation soluble chemic substances which remain in the serum and are not easily excreted from the vessels ("serotrope Stoffe"). The antisera are the most available for this purpose, since, according to the well-known investigations of Behring, they are retained a long time in the serum. It is comparatively easy to determine the degree of dilution which such bodies undergo in the circulation. For instance, 1 c.c. of tetanus antitoxin solution of known strength is injected into the circulation of an individual, and after allowing the blood to circulate a number of times in order to bring about a thorough mixture of the antitoxin, several cubic centimeters of blood are drawn from an arm vein. If the serum of this blood shows one-three-thousandth part of the antitoxic power of the undiluted substance, the total circulating serum must amount to 3000 c.c. and the entire blood to over 6000 c.c. In anemics the proportion by volume of the serum to the red blood-corpuscles must naturally be estimated for every individual case. In this way the amount of blood may be quite accurately measured in the living subject without any considerable difficulty.

[Haldane and Smith[1] have recently applied a method with considerable success. It is based upon the quantity of CO gas absorbed by the blood of a patient when a certain degree of saturation is obtained.

[1] *Jour. Physiol.*, vols. xxii. and xxv.; *Trans. Path. Soc.*, London, vol. li.

The patient is made to inhale a certain quantity of CO gas—*e. g.*, 100 c.c.; if the test sample of blood shows by their special method 20 per cent. saturation, the total capacity for CO is 500 c.c. The total quantity of blood is then determined by comparing the color of the patient's blood with that of ox blood of known capacity for CO absorption. If, for example, the color of the sample, as tested above, is the same as that of ox blood, 100 c.c. of which are capable of absorbing 20 c.c. of CO gas, the patient's blood contained 20 c.c. of CO gas in every 100 c.c. of his blood. To absorb 500 c.c. of CO his blood volume must therefore have been ($500 \div 20 =$) 25×100 c.c., or 2500 c.c. Using this method, the authors determined the total normal blood volume at from 2830 to 4550 gm., or one-thirtieth to one-sixteenth of the body weight.—ED.]

Number of Red Corpuscles.—There is no constituent of the blood which has been so accurately and regularly estimated as the number of red corpuscles in a cubic centimeter of blood. The simplicity of the counting apparatus commended the method. The most commonly employed are the Thoma-Zeiss and similarly constructed instruments, the principle of which may be assumed to be known. For the dilution of the blood a series of fluids have been proposed which are claimed to preserve the shape and color of the red blood-corpuscles, prevent rouleaux formation, and encourage rapid sedimentation. Among the well-known solutions, Pacini's and Hayem's may be mentioned:

Pacini's fluid:

Hydrarg. bichlor.	2.0
Sodii chlor.	4.0
Glycerin	26.0
Aqua destill.	226.0

Hayem's fluid:

Hydrarg. bichlor.	0.5
Sodii sulph.	5.0
Sodii chlorat.	1.0
Aqua destill.	200.0

The estimation of the white blood-corpuscles, which is carried out with a similar instrument, but as a rule with the blood diluted 10 instead of 100 times, requires a diluting fluid which destroys the red blood-corpuscles and makes the white more conspicuous by emphasizing their nuclei. The solution most adapted to this purpose is that recommended by Thoma, namely, about 0.5 per cent. acetic acid solution to which a trace of methyl-violet has been added.[1]

The results of this method of counting are exceedingly accurate in that A. R. Thoma and I. F. Lyon have shown that the probability of

[1] For the estimation of the proportion of the white to the red corpuscles, as well as of the individual forms to one another, see section on Morphology of the Blood.

error is only 5 per cent. on counting 200 cells, 2 per cent. for 1250, 1 per cent. for 5000, 0.5 per cent. for 20,000 cells.

In the practical application of the method factors come into consideration which modify the accuracy of the count. Cohnstein and Zuntz, and others, have shown that the blood of the larger vascular trunk is constant in composition, while that of small vessels and capilliaries may have considerable variations; for instance, the capillary blood may differ on the two sides in a hemiplegic, and stasis, cold, etc., may raise the number of red blood-corpuscles locally. In counting, therefore, the blood should be drawn only from parts of the body free from striking changes; all manipulation should be avoided which might change the capillary circulation, like rubbing, friction, etc.; and the examination should be undertaken at a time when the number of red blood-corpuscles is not influenced by digestion or medicaments.

The general practice is to take the blood from the tip of the finger, and only exceptionally—for instance, in case of edema of the fingers—from other places, like the lobe of the ear or the great toe (especially in children). A sharp needle or the open or concealed lancets constructed for the purpose are unnecessary; the author recommends most highly, in place of all complicated apparatuses, a new steel writing-pen, one prong of which has been broken off. Such a pen is readily disinfected by heating it in a flame, and with it, not a prick, but a more satisfactory open wound is obtained from which the blood flows freely without pressure.

The literature in regard to the estimation of red blood-corpuscles in health is almost unlimited. According to the recent statistics of Reinert and v. Limbeck, the following figures (reckoned per c.mm.) may be considered physiologic:

Men.

Maximum.	Minimum.	Average.
7,000,000	4,000,000	5,000,000

Women.

Maximum.	Minimum.	Average.
5,250,000	4,500,000	4,500,000

This difference between the sexes begins at the puberty of the female, up to which time (the beginning of menstruation) she possesses a somewhat larger number of red blood-corpuscles (Stierlin). Otherwise age seems to exercise no influence, except in the case of the newborn, when polycythemia (up to 8,500,000 during the first days of life) is regularly observed (E. Schiff). From the time of the first feeding this number gradually decreases to the normal, which is reached in from ten

to fourteen days. Now and again, according to Schmaltz, oligocythemia is observed in old age; yet this is not the rule, and must therefore be considered not a physiologic peculiarity, but a consequence of allied conditions.

The influence ordinarily exercised on the number of red blood-corpuscles by the taking of nourishment is attributable to the introduction of fluid, and is so slight that the deviations usually lie within the limits of technical error.

Other physiologic factors, like the first menstruation, pregnancy, and lactation, have no perceptible influence. There is also no difference between arterial and venous blood.

All fluctuations in the number of blood-corpuscles within the physiologic limit are, according to Cohnstein and Zuntz, dependent on vasomotor influences. Irritations by which peripheral vessels become narrower, lessen the number in that locality, while stimulation of the vaso-dilators produces the opposite effect. This would go to prove that the physiologic fluctuations of number in any locality are only the expression of a changed distribution of the red elements within the vessels, and are entirely independent of new formation and destruction of the cells.

Climatic conditions apparently have greater influence on the number of blood-corpuscles. This question is important from a physiologic, pathologic, and therapeutic standpoint, and has been brought to the foreground during recent years by Viault's investigations at the summit of the Cordilleras. From these researches, as well as from those of Mercier, Egger, Wolff, Köppe, v. Jaruntowski and Schröder, Miescher, Kündig, and others, it appears that the number of red blood-corpuscles in a healthy man with a normal average of 5,000,000 per c.mm., begins to increase immediately after arrival at a high altitude. After a gradual increase for about ten or fourteen days, a new average becomes established. This is in excess of the original average in accordance with the difference in height above the sea-level between the former and the present habitation. Moreover, individuals born and residing in olevated regions have a physiologic average in excess of that seen at sea-level, and this average is, as a rule, somewhat greater than that seen in the acclimatized—*i. e.*, those who reside only transiently at an elevation.

The following scale shows to what extent increase in height produces a deviation in the number of blood-corpuscles from the normal average (5,000,000).

Writer.	Place.	Height above sea-level.	Increase about
v. Jaruntowski.	Görbersdorf.	561 m.	800,000
Wolff and Köppe.	Reiboldsgrün.	700 m.	1,000,000
Egger.	Arosa.	1800 m.	2,000,000
Viault.	Cordilleras.	4392 m.	3,000,000

Exactly the opposite is seen when an individual with this high corpuscular count descends toward the sea-level.

This highly interesting phenomenon gave rise to different explanations and hypotheses. The immediate cause was first attributed to the lessened pressure of the higher air. Miescher especially made the lack of oxygen a specific stimulus for a new formation of erythrocytes. Omitting the physiologic improbability of such a rapid and comprehensive new formation, this explanation must be rejected because the histologic picture presents no proof (*i. e.*, excess of normoblasts). Köppe directed his investigations to the morphologic findings during acclimatization, and demonstrated that two processes completely independent of one another may be differentiated. He found simultaneously with the primary increase of red blood-discs numerous poikilocytes and microcytes. The increase therefore may be explained by the constriction and division of the red corpuscles already in the blood. On the basis of Ehrlich's explanation of poikilocytosis, Köppe sees in this process a physiologic adaptation to the lowered pressure of the air which makes the taking up of oxygen more difficult. This embarrassment of the function of the hemoglobin is to a certain extent compensated by the exposure of a greater surface, this resulting in increased respiration. It is thus easily understood why with the primary increase in corpuscles there is no increase in the percentage of hemoglobin or in the entire volume of the red blood-corpuscles. An increased formation of normal red blood-corpuscles first occurs during the second process, and naturally requires a longer period of time for its development. Corresponding to the degree of this new formation, the poikilocytes and microcytes disappear, so that eventually we have a blood characterized by an increased number of normal red blood-corpuscles together with a proportionate increase in hemoglobin and in volume of the corpuscular elements.

Other authorities assume only a relative and not an absolute increase of red blood-corpuscles. E. Grawitz has expressed the opinion that the increase in the number of corpuscles is entirely explained by an increased concentration of the blood, the result of an increased excretion of water at these heights. Animals experimented on by Grawitz in rarefied air seem to show this, yet v. Limbeck, and Schum-

burg and Zuntz contend that if the loss of water is so great as to cause such a considerable increase in the count, a corresponding diminution of body weight should be evident, which is not the case.

Schumburg and Zuntz also regard the increase of red blood-corpuscles on high mountains as relative, and explain it by an altered distribution of the corpuscular elements within the vascular system. In previous investigations Cohnstein and Zuntz demonstrated that the number of blood-corpuscles in the capillaries varies with the dilatation of the vessel and the rapidity of the blood-stream When one considers the numerous physiologic influences which may affect these factors, one must include them in explaining alterations in the number of the corpuscles. Moreover, on residence at high altitudes new factors come in to produce changes in the circulation and in the dilatation of the vessels. Among these factors may be mentioned intense light (clear atmosphere), lowering of the temperature, muscular effort, and increased activity of respiration. Considerable alterations may therefore occur in the number of the red blood-corpuscles in the capillary blood without the formation of microcytes and without formation of new cells.

The contradiction in those two views, namely, of Grawitz and of Zuntz and Schumburg, finds its explanation in the fact that both factors play important roles in the acute changes, though they become less conspicuous the longer the residence at a height (Viault). [Loez[1] also found that the increase of corpuscles so conspicuous at first partially disappears in two or three years. Natives of high altitudes stand midway between those of low altitudes and newcomers in higher places in the number of red corpuscles.—ED.] The conclusion therefore seems probable that on prolonged residence in a high region the number of red blood-corpuscles increases absolutely, a circumstance of considerable therapeutic importance.

[Stengel[2] thinks the probable explanation of the changed number of corpuscles may be found in vasomotor conditions and altered distribution of serum and corpuscles in the circulation.

Abderhalden[3] has made some studies in rats and guinea-pigs to determine the effect of elevation on the red corpuscles. He concluded that the increase in the number of the red corpuscles is not due to increased formation of these cells, and instances as proofs of this view both the rapid increase of the erythrocytes and hemoglobin in a high altitude, and the absence of any signs of increased formation of red

[1] *Phila. Med. Jour.*, 1900, p. 1074.
[2] "The Nature and Varieties of Anemia," *Jour. Amer. Med. Assoc.*, July 24, 1897.
[3] Inaug. Dissert., Basle, 1902.

cells in a high altitude or destruction of these cells on returning to a lower level, such as would occur if there were active destruction of corpuscles. His conclusion is that the theory of Bunge, that the increase of corpuscles results from a contraction of the vascular channels, is correct.

Campbell and Hoagland[1] found the number of erythrocytes increased about 50,000 for each 1000 feet of elevation. The pulse-rate keeps pace with the change in the blood, and they refer both alterations to the vasomotor disturbances resulting from reduced pressure. The lack of increase of hemoglobin corresponding to the increase in the number of corpuscles they think due to the fact that the preliminary increase in erythrocytes is only apparent. Later there are an actual increase in red cells and a corresponding increase in hemoglobin.—Ed.]

On the other hand, Gaule,[2] who found in aeronauts a marked increase in the red corpuscles to 8,800,000 at an elevation of 4600 meters, and a decrease in the hemoglobin, concludes that this is due to a new formation of red corpuscles, or at least is partly due to a new formation of red corpuscles and partly to an alteration of the old cells. On a second ascension he could demonstrate pictures of altered corpuscles such as are ordinarily observed in bone-marrow, in the embryo, and in certain diseased conditions.

In addition to altitude the influence of the tropics on the composition of the blood, especially the number of corpuscles, has been studied, and although the almost regularly pale appearance of Europeans in the tropics would point to alterations, Eykmann and Glogner found none. Here, too, mere changes in the distribution of the blood seem to play the principal rôle.

Less reliance can be placed on the Thoma-Zeiss and allied counting methods in anemic than in normal blood, in which, generally speaking, all red blood-cells are of the same size and contain the same amount of hemoglobin. In anemia, as will be seen later, the red blood-corpuscles are very dissimilar. On the one hand, an impoverishment of hemoglobin is found; on the other, very small forms which may pass unnoticed in the counting.

Moreover, omitting these extreme forms, 1000 red corpuscles of anemic blood would by no means correspond in their physiologic capability to an equal number from normal blood. It is therefore evident that the real value of the number of the red blood-corpuscles can not be estimated apart from the hemoglobinometric and histologic findings.

[1] *Amer. Jour. Med. Sci.*, 1901, cxxii., 6, p. 654.
[2] *Archiv. f. d. ges. Physiol.*, 1902, lxxxix., 3 u. 4, p. 119.

Separated from these, the mere count may lead to error, especially in pathologic conditions.

Relative Size of Red Corpuscles.—It is therefore desirable at times to supplement the results of the count by the determination of the size of the individual red blood-corpuscles. This is accomplished by the direct measurement of the diameter by means of an eye-piece micrometer, which can be employed both with dry (see below) and moist preparations, although generally employed with the former on account of the greater simplicity. Still, this requires a certain amount of careful technic. It is readily seen in dry preparations of normal blood that the red blood-corpuscles appear smaller when in thick layers than when more distributed. This is due to the fact that in the thick layer the red discs are surrounded by serum during their drying, while in thin preparations only a capillary layer of serum, attaching them to the underlying glass, is present. In the latter case the drying occurs almost instantaneously, so that a change of form or size can not occur, while the process of drying in the thicker parts proceeds more slowly, and is thereby more likely to be accompanied by shrinking.

[The size of the red corpuscles may be determined by accurate enumeration and estimation of the bulk of corpuscles in a given bulk of blood. The enumeration is carried out by the ordinary methods; the bulk, by centrifugation in accurately measured pipets. The range of error is necessarily great.—ED.]

Even in health a study of the blood will show slight differences in the individual blood-discs. The normal average diameter of the broad surface is, according to Laache, Hayem, Schumann, and others, in males and females, 8.5 μ (maximum, 9 μ; minimum, 6.5 μ). In anemic blood the differences between the individual elements is much greater, and the average is obtained by determining the maxima and minima of a large number of cells selected at random. When there is a high degree of dissimilarity, this estimation is devoid of scientific value.

Determination of the Hemoglobin.—Valuable as the knowledge of the absolute number of red blood-corpuscles is in the diagnosis of disease, it tells one nothing about the amount of hemoglobin in the blood, which is the decisive criterion of the degree of the anemia. For the determination of the hemoglobin we have a series of clinical methods, some direct, as the colorimetric, others indirect, as the estimation of the specific gravity, of the volume of the red blood-corpuscles, and of the dry residue of the blood.

Among the direct methods will be mentioned first one which makes

no great claim to accuracy, but which does good service in a rapid estimation at the bedside. The difference in color between anemic and healthy blood can be recognized more readily when it is allowed to spread in a thin layer on linen or filter-paper than when one merely observes the drops issuing from a finger-prick. With a little experience one can in this way roughly estimate the degree of the existing anemia. If this simple method, so readily carried out at the bedside, were commonly adopted, it would contribute much toward the overthrow of the popular diagnosis of "anemia." Moreover, in neurasthenics, who frequently appear anemic and persuade themselves that they are so, such a *demonstratio ad oculos* is frequently sufficient to convince them of the contrary.

[Tallqvist[1] has devised a simple method of testing the quantity of hemoglobin, based on the same principle. This consists in the comparison of a color scale on paper with the color produced on filter-paper by the application of a drop of blood. The color scale is arranged in a small book, and consists of ten distinct sections ranging from 10 per cent. to 100 per cent., and corresponding approximately to the Fleischl scale. A drop of blood is allowed to soak the edge of a piece of filter-paper specially prepared and furnished with the booklet, and the stain is then compared with the colors on the scale. The reading must be performed in daylight. Accuracy in reading may be enhanced by cutting a small circular hole through each of the sections of the color scale and applying the test back of this. The slightest deviation in color can then be readily detected. The defects of this method are that the colors are not constant, and that the variations of shades in the higher percentages are so slight as to make an accurate reading practically impossible.—ED.]

Among the instruments for measuring the coloring-matter of the blood, "Hoppe-Seyler's colorimetric double pipet" is probably the best; in this an accurately titrated solution of carbonic-oxid-hemoglobin serves for comparison. The preparation and preservation of such a standard solution, however, are attended with such difficulties that this method can not be reckoned among the clinical ones which will be considered. Lately Zangemeister, a pupil of Kühne's, has proposed an apparatus for colorimetric purposes, adaptable for hemoglobin. It depends on the principle that the amount of coloring-matter can be estimated from the thickness of the layer required to make the trial solution correspond in color to the standard solution. He employs as a standard a methemoglobin-glycerin solution made from hogs' blood. As far as the author knows, this important method has not been adopted

[1] *Zeitschr. f. klin. Med.*, 1900, Bd. xl. Hefte 1 u. 2.

in practice. For the present, the most useful methods are those in which colored glass or solutions which retain their color are employed as standards. There are a large number of these, though the most commonly used are Fleischl's "hemometer," and on account of its low price Gowers' "hemoglobinometer." Both instruments show the percentage of hemoglobin in comparison with normal, and are for practical purposes sufficiently accurate even though in inexperienced hands errors of 10 per cent. or more occur (K. H. Mayer).

[Dare[1] has devised a simple and reliable instrument having the advantage that undiluted blood is compared with a disc of colored glass. The blood is allowed to flow between two small plates of glass, one transparent and the other white and translucent. The color of this film is compared with that of a disc of colored glass, which may be rotated back of the blood-containing plates and in front of a candle used for illumination. The ease of operation and the fact that the examination can be made without exclusion of surrounding light are important advantages.—ED.]

Very recently Biernacki objected to the quantitative estimation of hemoglobin by the colorimetric methods because the coloring power of the blood does not depend alone on the amount of hemoglobin that it contains, but also on the staining of the plasma and the greater or less quantity of albumin in the blood. This objection is valueless as far as the apparatuses in question are concerned, since the blood is so diluted with water that the differences originally present are reduced to *nil*.

Among the indirect methods of estimating the amount of hemoglobin that which determines it from the amount of iron in the blood may be considered quite accurate, since hemoglobin possesses a constant percentage of iron (0.42 per cent.). This method is undoubtedly justifiable for normal blood in which there is a constant proportion between the hemoglobin and the amount of iron. A. Jolles recently proposed an apparatus ("ferrometer") which estimates rapidly and exactly the amount of iron in small quantities of blood.

In pathologic cases, however, this method of estimating the hemoglobin is not advisable. If anemic blood is tested under the microscope with proper reagents, an iron reaction may be found in numerous red blood-corpuscles, which shows the presence of iron besides that which is a constituent of the hemoglobin. Moreover, other iron may be contained in the morphologic elements, even the white blood-corpuscles, in forms not certainly demonstrable as combinations with albumin. Further, it is known that the amount of iron in the organs is increased in

[1] *Phila. Med. Jour.*, 1900.

anemia (Quincke), though frequently as an expression of increased destruction of hemoglobin ("débris iron," "spondogenous iron"). The thought naturally arises, too, that the medical administration of iron may increase the amount of iron in the blood and in the organs. It is therefore evident how unsatisfactory in pathologic cases is the estimation of hemoglobin from the amount of iron.

The author is forced to insist on this matter on account of the very strange conclusions arrived at by Biernacki from making the amount of iron a criterion for the amount of hemoglobin in the blood. He found, for instance, the iron quite normal in two mild and one severe case of chlorosis, and jumped to the conclusion that chlorosis—as well as other anemias—showed no diminution, but rather a relative increase in the hemoglobin, while other albumins of the blood were decreased. Even if these iron estimations, which are very different from those of other investigators, were entirely reliable, which could be assumed only by the most careful repetition of the experiments, the broad conclusions drawn by Biernacki were unjustified. Thorough investigations with the aid of Jolles' ferrometer would be desirable in these cases.

Specific Gravity.—Considerable significance has long been attributed to the specific gravity of the blood, since the thickness of the blood is a criterion for the number of corpuscles and the amount of hemoglobin. Numerous experiments in this direction are at hand, since in late years two methods have been introduced which require but little material and are not too complicated for practical clinical purposes. The first was suggested by R. Schmaltz, and consists in the weighing of small quantities of blood in glass capillary tubes ("capillary pycnometric method"); the other by A. Hammerschlag, who, varying the principle proposed by Fano, experiments till he finds a mixture of chloroform and benzol in which a drop of the blood to be examined will neither rise to the top nor sink to the bottom, in other words, which accurately represents the specific gravity of the examined blood.

From the investigations of these and numerous others who have used the methods, the specific gravity of the blood was found to be normally 1058 to 1062, or on an average 1059 (in women, 1056); the specific gravity of the serum, 1029 to 1032, or an average of 1030. From this it is evident that the red blood-corpuscles are responsible for the greater part of the weight of the blood. Therefore, if they lessen in number or if they remain the same but lose in hemoglobin or volume, these changes will produce a corresponding decrease in the specific gravity. Consequently one would expect in all anemic conditions a

lessened specific gravity. Reversely, with increase in the number of corpuscles or a higher hemoglobin content there is an increase in the thickness of the entire blood.

Hammerschlag, from a large series of experiments, has demonstrated that the relation between the specific gravity and the amount of hemoglobin is much closer than that between the specific gravity and the number of corpuscles; in fact, the former is so constant as to allow a graphic representation:

Specific gravity.	Amount of hemoglobin (according to Fleischl).
1033–1035	25–30 per cent.
1035–1038	30–35 "
1038–1040	35–40 "
1040–1045	40–45 "
1045–1048	45–55 "
1048–1050	55–65 "
1050–1053	65–70 "
1053–1055	70–75 "
1055–1057	75–85 "
1057–1060	85–95 "

In a very recent work Dieballa devoted particular attention to these relations. His results sometimes confirm Hammerschlag's, or again supplement them. He obtained from his comparative estimations an average which showed that differences of 10 per cent. hemoglobin (Fleischl) in general correspond to differences of 4.46 pro mille specific gravity (Hammerschlag's method). Yet with exactly similar amounts of hemoglobin, differences in specific gravity up to 13.5 pro mille are demonstrable, and these deviations are greater the greater the amount of hemoglobin in the blood. Regular differences exist between men and women, the latter showing, with an equal amount of hemoglobin, a specific gravity of 2 to 2.5 less. If the correspondence between the number of red blood-corpuscles and the amount of hemoglobin is markedly disturbed, the influence of the stroma of the red disc on the specific gravity is noticeable. Dieballa reckons that the stroma can produce differences in the specific gravity of 4 to 5 pro mille in two cases showing the same amount of hemoglobin. [Yarrow,[1] however, found that the table was quite accurate when used with reference to a standard solution of hemoglobin made by dissolving 13.77 gm. in normal salt solution to make 100 gm.—Ed.]

The estimation of the specific gravity is therefore frequently sufficient to indicate the relative amount of hemoglobin. In nephritis and circulatory disturbances, as well as in leukemia, the relation between the specific gravity and the amount of hemoglobin is seriously influenced by other factors.

[1] *Univ. Med. Mag.*, 1899.

The physiologic fluctuations of specific gravity in the same individual under the influence of the introduction and excretion of fluid do not exceed 0.003 (Schmaltz). From what has been said, these correspond to the fluctuations to which the amount of hemoglobin and the number of corpuscles are subject, and come into existence only with them.

Later investigations, especially those of Hammerschlag, v. Jaksch, v. Limbeck, Biernacki, Dunin, E. Grawitz, and A. Löwy, have supplied an omission of earlier workers in that besides the specific gravity of the blood as a whole, they have studied the specific gravity of at least one of its constituents, namely, the corpuscles of the serum. All are unanimous in the view that the red blood-corpuscles are almost exclusively responsible for the fluctuations in specific gravity of the blood as a whole, partly on account of their fluctuations in number or changes in distribution, partly on account of their chemic instability, namely, loss and increase of water, and fluctuations in the amount of albumin. The fluid of the blood, on the contrary—and here there is no particular difference between plasma and serum (Hammerschlag)—shows a much greater constancy. Even in severe pathologic conditions in which the blood is specifically much lighter, the serum preserves its physiologic composition or undergoes only comparatively slight fluctuations in concentration. A great decrease in specific gravity of the serum is much less frequently observed in specific blood diseases than in chronic diseases of the kidney and circulatory disturbances. Still more recently E. Grawitz has shown that the specific gravity of the serum suffers marked decrease in certain anemias, especially the post-hemorrhagic and those due to inanition. Despite a few contradictions, it is evident from these observations that in a scientific investigation the specific gravity of the serum and the corpuscles should be correlated with that of the entire blood.

A method closely related to the estimation of the specific gravity, introduced into practice by Stintzing and Gumprecht, is sometimes employed, especially since it can be carried out with small quantities of blood such as frequently must be made use of in practice. This method is the direct estimation of the dried substance of the blood, **hygromometry.** Small amounts of blood are received in small weighing-vessels, weighed, dried for twenty-four hours at 65°–70° C., and weighed again. The figures so obtained possess a certain independent significance, since they do not correspond exactly with the specific gravity, the amount of hemoglobin, or the number of corpuscles. Normally in men we find 21.6 per cent. of dry residue; in women, 19.8 per cent.

Percentage Volume of Red Corpuscles.—A further indirect procedure for obtaining the amount of hemoglobin is the determination of the percentage volume of the red corpuscles in comparison with the whole blood. For this a method is necessary which separates the corpuscles from the blood in an unchanged condition. The older methods failed in that they either required a previous defibrination of the blood (which is, as a rule, impossible in the small amounts at our disposal in practice), or the addition of sodium oxalate or other substances, to prevent clotting. The separation of the two constituents was brought about by simple sedimentation or by the help of centrifuges, especially constructed for the blood by Blik-Heiden and Gärtner (*hematocrit*).

The many diluting fluids like physiologic salt solution, 2.5 per cent. potassium bichromate solution, and others are, according to H. Köppe, not indifferent toward the red blood-corpuscles, and a solution incapable of altering the cells must be especially prepared for every blood. Considerable attention, therefore, was devoted to the procedure of M. Herz, in which the coagulation of the blood in the pipet is prevented by making its walls absolutely smooth by means of codliver oil. This procedure has been modified somewhat by Köppe. He fills his very practical pipet, after careful cleaning, with cedar oil, and then draws up the blood issuing from the finger wound, which, forcing the oil before it, remains fluid on account of coming in contact with perfectly smooth walls. With the aid of his modified centrifuge the oil, as a lighter substance, is completely removed from the blood and the plasma separated from the corpuscles. Three sharply limited layers are thus produced, namely, a layer of oil, of plasma, and of red blood-corpuscles. Since the apparatus is graduated, the volume of plasma and corpuscles can at once be read off. Microscopically the corpuscles are found unaltered.

Though this procedure appears difficult, it is the only one from which clinical pathology has anything to expect. Köppe's results, though rather limited in number, show the entire volume of the red blood-corpuscles to be 51.1 to 54.8 per cent., or on an average 52.6 per cent.

M. and L. Bleibtreu endeavored in an indirect way to determine the relation of the volume of the red blood-corpuscles to that of the plasma. They made different mixtures of blood with physiologic salt solution, determined in each the percentage of nitrogen in the fluid separated from the corpuscles by sedimentation, and with the aid of these comparative quantities estimated the volume of blood-serum and of red

blood-corpuscles. Omitting the fact that dilution of the blood with salt solution is necessary, this method is too complicated and requires too large amounts of blood to be practicable in the clinic. Th. Pfeiffer endeavored to employ it in selected cases without so far obtaining very definite results. Moreover, the relation between the percentage volume of red blood-corpuscles and the amount of hemoglobin is by no means constant, as is proved, for instance, by the circumstance that in acute anemia an "acute swelling" of the individual red blood-discs (M. Hertz) occurs which could produce an increase in volume without a corresponding increase in the amount of hemoglobin. This is also seen from the recent observations of v. Limbeck, who found a considerable increase in the volume of the red blood-corpuscles in catarrhal jaundice, due to influence of the salts of the biliary acids.

As the writer has several times declared, the estimation of the hemoglobin is the most important criterion for the severity of an anemic condition. The investigations of the blood which indicate neither directly nor indirectly the amount of hemoglobin, are of interest only in as far as the pathogenesis of special cases is concerned. Among these we have the estimation of the **alkalinity of the blood,** which, in spite of extensive observations, is so far of no significance in the pathology of blood diseases.

Coagulability of the Blood.—An estimation to which perhaps more attention will be devoted than has yet been given it by the clinician, is that of the rapidity of coagulation. Good comparative results are obtained by the aid of Wright's convenient "coagulometer." In certain conditions, especially in the acute exanthemata, and different forms of the hemorrhagic diathesis, the time of coagulation is decidedly lengthened, even to possible failure of coagulation. In other conditions there may be an evident hastening of coagulation in comparison with the normal. Moreover, Wright determined, in his excellently carried out investigations, that an influence may be exercised by medicaments: for instance, calcium chlorid and carbonic acid increase, citric acid, alcohol, and rapid respiration diminish the coagulability.

A condition recently described by Hayem probably stands in close relation to this change of coagulability. He discovered that in spite of coagulation a **separation of the serum from the clot** sometimes fails to occur, or occurs to only a slight degree. He found this condition in purpura hæmorrhagica, protopathic pernicious anemia, malarial cachexia, and several infectious diseases. For these investigations large amounts of blood are necessary, which are not at our disposal in practical work. Certain precautions, learned by experience in

obtaining diphtheria serum, must be attended to in order that the amount of serum be as large as possible. For instance, the blood should be caught in high vessels that have been carefully cleaned and freed from every trace of fat. If the clot does not spontaneously retract at once, it must be loosened, without breaking it, with a flat, paper-knife-like instrument, from the side of the glass. If no separation results in the cold, the blood may be put into an incubator.

In spite of every artificial contrivance and care it now and then happens under pathologic conditions that not a trace of serum is obtained from a large amount of blood. So, for instance, Ehrlich obtained scarcely 100 c.c. of serum from 22 kg. of horse blood after the animal had been bled on account of tetanus, though the animal had previously furnished an extraordinary amount of diphtheria serum.

A conspicuous rôle in the study of blood diseases will possibly yet be attributed to these phenomena. Hayem even now proposes defective serum formation as a differential point between protopathic pernicious and other severe anemias, and asserts that it is an unfavorable prognostic sign when this phenomenon is observed, for instance, in cachectic conditions.

Mention has still to be made of several methods which show the **resistance of the red blood-corpuscles** to external injuries of various kinds.

Landois, Hamburger, and v. Limbeck determine, for example, the concentration of the salt solution required to preserve the red blood-corpuscles ("isotonic concentration," Hamburger), and that which removes the hemoglobin from the stroma. The erythrocytes are the more resistant the less the concentration required to preserve them.

Laker determines the resisting power of the red blood-corpuscles to electric discharges from a Leyden jar, and measures it according to the number of discharges which prove innocuous.

Clinical medicine has so far obtained but little from these methods. This only is assured, that in certain diseases like anemia, hemoglobinuria, and many intoxications, the resistance of the red blood-corpuscles measured by these means is decidedly decreased.

MORPHOLOGY OF THE BLOOD.

METHODS OF EXAMINATION.

A GLANCE into the history of the microscopy of the blood shows that it is divisible into two periods. In the first period, which is especially characterized by the work of Virchow and Max. Schultze, a number of positive facts were collected, particularly in relation to the different forms of leukemia, but an interruption soon occurred which continued throughout a decennium on account of the fact that the investigations were limited to the examination of the fresh blood. All that was to be learned by this simple method was completely exhausted in a short time by the zeal of the investigators. That this method was inadequate is most readily seen from the history of leukocytosis, which condition was referred by Virchow to an increased production of leukocytes by the lymph-glands, and from the uncertain differentiation of leukocytosis and beginning leukemia, which was based almost exclusively on the estimation of the number of white corpuscles. The histology of the blood entered on its second period after Ehrlich's introduction of the new methods of examination of stained preparations. To these methods we owe the accurate differentiation of the different kinds of white blood-corpuscles, the rational differentiation of leukemia and of polynuclear leukocytosis, and the knowledge of the signs of degeneration and regeneration in the red blood-corpuscles. In the study of the blood, therefore, the same advance took place as in the other chapters of normal and pathologic histology, namely, a marked increase in knowledge with improvements in technic. It is consequently difficult to understand how, at the present day, a writer can recommend a return to the old methods, declaring that the diagnosis of any case is possible from the examination of the fresh blood alone. This is undoubtedly no great feat in the majority of cases, since the most important points have now been made clear by the new methods. Still, for more difficult cases (for instance, the early diagnosis of malignant lymphoma, of certain rare forms of anemia, etc.) the stained preparation is indispensable. Moreover, it may be added that the purpose of

a blood examination is not the making of a rapid diagnosis, but the exact investigation of the blood-picture in all its details, and this can not be done with unstained blood. The only standpoint possible today is that everything which can be seen in the fresh preparation—excepting the clinically unimportant rouleaux formation and ameboid movement—can be studied much better in the stained preparation, while in addition there are many important details which become visible only in the latter.

As far as the mere practical technic is concerned, the examination of stained preparations is undoubtedly much less troublesome. It leaves one entirely independent as to place and time of examination. The dried blood can, with slight precautions, be preserved for months before applying further microscopic technic. The examination may extend over any length of time, and may be repeated at will. The study of the fresh blood, on the contrary, must be made at the bedside, and on account of the alterations in the blood, clotting, disturbances of the white blood-corpuscles, etc., it must be examined so quickly that a thorough investigation is impossible. When we add to this, that the method of staining the dried preparation is one of the most simple in clinical histology, it is no more than right, in the interest of its further dissemination, to describe it thoroughly.

We must likewise not forget the employment of the dry preparation in the determination of the numerical relation of the red to the white blood-corpuscles, and of the white blood-corpuscles to one another.

For these determinations faultlessly made and regularly spread preparations are an absolute essential. Moreover, we require square ocular blends (Ehrlich-Zeiss) which present a section the sides of which are 1 : 2 : 3 . . . . . . : 10, and the whole section 1 : 4 : 9 . . . . . . : 100; or the more satisfactory "ocular" made by Leitz from Ehrlich's instructions, in which a central square field of known proportions is readily obtained by a handy mechanism. A normal preparation, for instance, is studied as follows: The white blood-corpuscles are counted in any section made by the blend number 10 (ocular section 100), and without moving the field, the ocular blend number 1–2 comprehending, therefore, only the one-hundredth part of the former, is set in place and the red blood-corpuscles counted. The preparation is then moved and the red blood-corpuscles repeatedly counted in a section one-one-hundredth or one-twenty-fifth that of the whites. About one hundred such counts are made in one preparation. The sum of the reds is then multiplied by 100 and the proportion of this figure to the sum of the whites is determined. If the white blood-corpuscles are very numerous, so

that the counting of every one in a large field is too troublesome, one of the smaller ocular sections, 81, 64, 49, etc., is taken.

The determination of the percentage proportion of the different leukocytes is made by counting and classifying several hundred cells, a matter which the expert can complete in less than a quarter of an hour.

PREPARATION OF A DRIED SPECIMEN.

Primary essentials in the preparation of perfect specimens are cover-glasses of a special quality. These must not be thicker than 0.08 to 0.10 mm., must not be rough or loamy, and must bend easily without breaking. The slightest inequality renders them unsuitable. They must be carefully cleaned, and especially every particle of fat must be removed. It is ordinarily sufficient to place them separately in ether for about half an hour, and to wipe them dry, while still moist with ether, with a piece of soft linen free from lint or with Josefspaper. Following this they are placed for several minutes in alcohol, are dried as before, and are then preserved in dust-proof glass vessels till wanted. When it is remembered that these cover-glasses are cut in oil, it is evident that only when so prepared will a capillary space be formed between them in which the blood can readily spread, and only then can they be readily drawn apart from one another without the employment of an injurious force.

In order to prevent soiling the cover-glasses anew, and especially to prevent the contact of the blood with the moisture from the finger, the cover-glasses are held in forceps while taking the blood. For the under cover-glass the writer recommends a sliding forceps with smooth broad arms, the ends of which are covered for about 3 cm. with leather or filter-paper; for the other a very light pen-like forceps, with smooth arms of almost knife-like sharpness anteriorly, by means of which a cover-glass may be readily picked up from a smooth surface. The under cover-glass is now seized by the margin in the sliding forceps and held ready in the left hand; the right hand brings the cover-glass in forceps in contact with the drop of blood without allowing it to touch the finger. This cover-glass is then quickly but lightly placed on the other, when the drop spreads in an even capillary layer. The margin of the upper cover-glass is now seized with two fingers of the right hand and carefully slid off the under one without pressure or elevation. Often only the under one shows a completely regular distribution, though sometimes both are serviceable. While drying in the air, which takes from ten to thirty seconds, the preparations must naturally be protected from moisture (for instance, from the breath of patients standing near).

How much of the surface is covered depends on the size of the drop: the smaller the drop, the smaller naturally the surface of distribution. Too large drops, causing one cover-glass to swim on, rather than adhere to, the other, are useless.

Though the written description of these manipulations may appear somewhat complicated, but little practice is required to perform them with dexterity and accuracy. The author has repeated the technic so exactly because he has frequently seen preparations technically unsatisfactory although made by investigators who were specialists in hematology.

After the preparations are entirely dry they are preserved between layers of filter-paper in well-closed vessels till wanted. In important cases, when

it is desirable to preserve the preparations for a long time, it is recommended to protect some of the specimens from atmospheric influences, by covering them with a layer of paraffin. In this case, previous to further manipulation the paraffin covering must be dissolved off with toluol. The preparations must naturally be preserved in the dark.

FIXATION OF DRY PREPARATIONS.

All the methods of staining require a previous fixation of the albumin of the blood. A general method of fixation can not be given, since its intensity must be made dependent on the staining methods selected. For staining by simple watery solutions—*e. g.*, triacid solution—a comparatively slight degree of fixation is sufficient, and this may be obtained by a short exposure to different agents. In the case of other methods in which strong acid solutions or those containing a free alkali are employed, it is necessary to fix the structure by much stronger agents, though even here a warning must be given against excess. On account of the small number of staining solutions it is easy to determine the optimum for each.

The following are the common methods of fixation :

Dry Heat.—A simple copper plate on a tripod, under one end of which a Bunsen flame burns, is employed. After heating some time a certain constancy in the temperature of the plate is obtained, the portion nearest the flame being naturally the hottest, that furthest away least warm. By dropping on water, toluol, xylol, etc., it is easy to determine the point at which the plate shows the boiling temperatures of these fluids.

Victor Mayer's apparatus, commonly used by chemists, is much more practical. Suitably modified to our purpose, this consists of a small copper kettle, the lid of which makes a copper plate which is penetrated only by an opening for the steam pipe. If small amounts of oil of tolu are allowed to boil in this kettle for several minutes, the copper plate will be found to take on a temperature of 107° to 110° C.

For ordinary staining (by watery solutions) it is sufficient to expose the preparations dried in the air to a temperature of about 110° C. for one-half to two minutes. For other staining mixtures—*e. g.*, eosin-aurantia-nigrosin—a fixation of one to two hours or a higher temperature is required.

Chemic Agents.—(*a*) According to Nikiforoff, a good triacid stain may be obtained after hardening the preparation for two hours in a mixture of equal parts of *absolute alcohol and ether*. Still, such preparations do not reach the perfection of those fixed by heat.

(*b*) *Absolute alcohol* fixes the dried preparation within five minutes

sufficiently to stain with Chenzinsky's fluid, or hematoxylin-eosin solution. In some cases where it is necessary to make the examination rapidly, it is of advantage to boil the preparation one minute in absolute alcohol in a watch-glass.

(*c*) *Formol* in a 1 per cent. alcoholic solution was first employed by Benario for the fixation of blood preparations. Fixation is sufficiently complete in one minute to show the granulations. Benario recommends this method especially when staining with hematoxylin-eosin.

It is unnecessary to state that these methods are described as the most suitable only for general blood examinations. For special purposes, for instance, the illustration of mitoses, blood-platelets, etc., other methods of fixation, as sublimate, osmic acid, Flemming's solution, etc., are more serviceable.

STAINING OF DRY PREPARATIONS.

The different stains can be classified according to the purpose for which they are employed.

We turn first to those which produce rapid pictures suitable for general study; in other words, dyes which stain simultaneously the hemoglobin and the nuclei (hematoxylin-eosin, hematoxylin-orange).

Again, a stain is desirable which brings out a particular variety of cell, for instance, eosinophiles, mast-cells, bacteria. This is called "single staining," and is produced by decolorization (see E. Westphal).

Finally, we have the panoptic stain—that is, one which stains a large number of elements in different tints. This method is of particular utility for a complete investigation. When in addition the preparation is studied by the strongest powers, we are able to analyze it with a thoroughness otherwise impossible. In order to make a complete differentiation we should not be content with double staining, but should employ at least three different stains. Formerly this was accomplished almost exclusively by successive staining, yet any one who has tried this method appreciates the difficulties in obtaining constant results even after the closest observance of the prescribed details in regard to the duration of the staining and the concentration of the solutions.

In contrast to the above the method of simultaneous **combined staining** is technically simple, and its advantages have been demonstrated. Since there is considerable obscurity surrounding its principle, the details of the theory of differential simultaneous staining will be briefly given.

For this purpose a very simple example will be discussed, namely, the employment of picrocarmin—that is, a mixture of neutral ammonio-

carmin and a picric acid salt. If tissue rich in protoplasm is stained with this carmin solution, the carmin is found to stain pretty diffusely, though the nuclei stand out prominently. Still, if an equally concentrated solution of picric acid ammonia is added, the staining becomes much more distinct in that certain parts are pure yellow, others pure red. The best example is the staining of muscle by picrocarmin, when the muscle-substance appears yellow, the nuclei red. If, however, instead of the picric acid ammonia another nitro stain is added which contains more of the nitro groups than the picric acid, for instance, the ammonium salt of hexanitrodiphenylamin, the carmin fails to stain and all parts take an orange color, entirely independently of the duration of the staining. The explanation of this is not difficult. Myosin has a greater affinity for picric acid ammonia than for carmin salts, and from a mixture of both components, therefore, takes to itself the yellow coloring-matter. After this combination it is impossible for the carmin to act. The nuclei, on the contrary, have a greater affinity for carmin, and stain, therefore, pure red. But if a nitro stain is added to the carmin solution which has a greater chemic affinity for all tissues, nuclei included, the effectiveness of the carmin is reduced; and if a very strong nitro body, a hexanitro combination, is added, the action of the carmin completely disappears. Connective tissue, bone, and similar tissues behave very differently to mixtures of picrocarmin, in that in these cases the diffuse staining is entirely dependent on the concentration (or dilution) of the carmin, and is not at all influenced by the chemic contrast-stains. This method of staining, therefore, must be regarded not as a chemic combination, but as a mechanical attraction for the stain on the part of the tissues. Consequently chemic staining may be described as that in which the tissues react to chemic contrasts, and mechanical staining in which they react to physical modifications. This statement naturally presupposes that we are dealing with pure neutral stains, and it excludes all additions like alkalis and acids which change the chemic behavior of the tissue, as well as such as increase or decrease the affinity of the stain for the tissue. The result of this is that any successive double staining can be replaced by a combination staining if the chemic nature of the process is determined, in contrast to the double staining brought about by mechanical factors which can be accomplished only by successive staining.

In the staining of dry blood preparations pure chemic processes are concerned, and it is consequently possible in every case to employ the polychromatic combination stains.

The following combinations may be employed in staining the blood:

1. *Combination-staining with Acid Stains.*—The best known example is the eosin-aurantia-nigrosin mixture, with which the hemoglobin is stained orange, the nuclei black, and the acidophile granulations red.

2. *Mixtures of Basic Stains.*—It is a simple matter to compound a stain from two basic stains. As especially suitable may be mentioned fuchsin, methyl-green, methyl-violet, methylene-blue. The compounding, however, of a mixture from three basic stains is somewhat difficult, and requires careful attention to quantitative proportions. For such mixtures fuchsin, Bismarck-brown, and chrome-green may be employed.

3. *Neutral Mixtures.*—These were introduced into hematology by Ehrlich, have recently come to play an important rôle in general histology, and deserve therefore more detailed consideration.

Neutral staining depends on the fact that almost all basic stains (*i. e.*, salts of the basic stains, for instance, acetic acid rosanilin) combine with acid stains (*i. e.*, salts of the acid stains, for instance, picrate of ammonium), and make what may be characterized as neutral stains, like picric acid rosanilin. Their employment is rendered more difficult on account of the fact that they are but slightly soluble in water. They became practical only after Ehrlich had found that certain series of the neutral stains were readily soluble in an excess of the acid stain, which made it possible to obtain stable solutions of any concentration. Among the basic stains suitable may be mentioned especially those which contain the so-called ammonium group, particularly methyl-green, methylene-blue, amethyst-violet (tetraethyl-safranin-chlorid), and to a certain extent pyronin and rhodamin. In contrast to these, with the exception of methyl-green, the members of the triphenylmethan group, for instance, fuchsin, methyl-violet, Bismarck-brown, phosphin, indazin, are generally less suitable for this purpose. Among the acid stains, it is especially the readily soluble salts of the polysulpho-acids which are adapted for the compounding of soluble neutral stains, while the salts of carbonic acid and the phenol stains are only to a slight degree suitable, and least suitable of all are the nitro stains. From the series of acid stains may be mentioned especially orange-G, acid fuchsin, and narcein (a readily soluble yellow stain, the sodium salt of sulphanilic-acid-hydrozo-β-naphtol-sulphonic acid).

Triacid Staining.—If a solution of an acid stain, for instance, orange-G, is poured drop by drop into a solution of methyl-green, a coarse precipitate first occurs which dissolves on the further addition of the orange solution. In fact, the solution should be prepared so that no more orange is added than is necessary to complete solution. This is a type of a simple neutral staining solution. To explain this

example chemically, we must believe that all three basic groups of the methyl-green in this mixture are in combination with the acid stain; in other words, that we have to do with a *triacid* combination of the methyl-green.

Simple neutral mixtures having one common constituent readily enter into combination with one another. This is a very important fact in the practical and valuable triple stain. This is made only by mixing two simple neutral mixtures,—that is, two mixtures consisting of two components with one another; chemic decomposition need not be feared. Thus are obtained the important practical solutions which contain three or more stains. Theoretically there are two possible combinations:

1. Mixtures consisting of one acid and two basic stains: orange-amethyst-methyl-green; narcein-pyronin-methyl-green; narcein-pyronin-methylene-blue.

2. Mixtures consisting of two acids and one base: orange-G acid fuchsin-methyl-green; narcein-acid fuchsin-methyl-green.

3. The corresponding combinations of methylene-blue and amethyst-violet. The first of these will be described more in detail later.

The importance of these neutral stains lies in the fact that they stain certain definite elements which are not stained by the different components, and which are described therefore as neutrophile.

Elements which like nuclear matter have an affinity for basic stains are stained by the basic stains in these neutral mixtures, acidophile elements by one of the two acid stains, while those which possess a simultaneous affinity for acids and basic stains take up the neutral stain as such and stain therefore a mixed color.

The *eosin-methylene-blue mixture* shows a certain contrast to the common staining mixtures, inasmuch as with an excess of the basic methylene-blue there is still sufficient eosin solution to make both stains active. An objection to such a mixture is that precipitates readily form in it, making the preparation unserviceable. This is most likely to occur in freshly prepared solutions, to which the components have just been added, and least likely in solutions like Chenzinsky's, which may be preserved for a long time. Still, fresh solutions stain much more intensely and diversely, and must be employed in special cases (see pages 44, 45). When the stain has succeeded, the picture is extremely instructive. The nuclei are blue, the hemoglobin red, the neutrophile granulations violet, the acidophile pure red, and the mast-cell granulations intensely blue; —one of the prettiest microscopic pictures that it is possible to see.

For practical use, besides the iodin and iodin-eosin solution which will be described later (pages 45 and 46), there are the following:

1. *Hematoxylin solutions with eosin or orange-G.*

Eosin (cryst.)	0.5.
Hematoxylin	2.0.
Absolute alcohol,	
Aqua dest.,	
Glycerin	āā 100.0.
Acid. acet. glac.	10.0.
Alum in excess.	

Several weeks are required for the solution to ripen. Preparations fixed in absolute alcohol or by heat are stained in one-half to two hours; the hemoglobin and the acidophile granulations are red, the nuclei the color of the hematoxylin. The stain must be very carefully washed off.

2. In the *practical employment of the triacid solution* it is important, as was first demonstrated by M. Heidenhain, that the stains be chemically pure.

The advantage of the solution prepared from these stains is evident from the fact that basophile granulations in the neighborhood of the nucleus of the white blood-corpuscles are not now frequently found; these were once regarded by even experienced investigators (*e.g.*, Neusser), not as artefacts, but as preformed perinuclear formations, though their significance could not be explained.

Saturated watery solutions of the three stains are prepared and cleared by long standing. They are then mixed in the following way:

Orange-G solution	13–14 c.c.
Acid fuchsin solution	6– 7 "
Aqua dest.	15 "
Alcohol	15 "
Methyl-green	12.5 "
Alcohol	10 "
Glycerin	10 "

These substances are measured in the prescribed order by the aid of a graduated glass, and, after the addition of the methyl-green, thoroughly shaken. The solution is at once ready for use, and can be preserved a long time. Slight fixation only is necessary (see page 38). Staining is complete in at most five minutes.

The nuclei are greenish, the red blood-corpuscles orange, the acidophile granulations copper colored, and the neutrophile violet. The mast-cells become conspicuous on account of a "negative staining" as peculiar clear, almost white cells, with pale-green nuclei.

The technic of triacid staining is therefore extremely simple. The stain is very satisfactory for general study, and is indispensable in all cases where the neutrophile granulations come into consideration.

3. *Basic Double Staining.*—Saturated watery methyl-green solution is mixed with a dilute alcoholic fuchsin solution.

The staining, which also requires only slight fixation, is complete in a few minutes; the nuclei are green, the red blood-corpuscles red, and the protoplasm of the lymphocytes fuchsin colored. It is very suitable therefore for demonstrating specimens of lymphatic leukemia.

4. *Eosin-methylene-blue mixtures—e. g., Chenzinsky's fluid:*

Concentrated aqueous methylene-blue solution	40 c.c.
0.5 per cent. eosin solution in 70 per cent. alcohol	20 "
Aqua dest.	40 "

The solution is quite stable, though before use it must always be filtered. It requires only fixation of the preparation in alcohol for five minutes. Six to twenty-four hours in an air-tight vessel in an incubator are required for staining.

The nuclei and the mast-cell granulations are stained intensely blue, malarial plasmodia a delicate sky blue, the red blood-corpuscles and the eosinophile granulations a beautiful red.

This solution is therefore recommended for the study of the structure of the nuclei, of the basophile and eosinophile granulations, and is employed with advantage in anemia as well as lymphatic leukemia.

5. 10 c.c. of a 1 per cent. aqueous solution of eosin are mixed with 8 c.c. of *methyl-alcohol* and 10 c.c. of a saturated watery solution of medicinal *methylene-blue,* and the mixture is at once ready for use (see page 27). The duration of staining is one, at most two minutes. Staining is successful only when the preparations are carefully fixed by heat. The mast-cell granulations are stained pure blue, the eosinophile red, the neutrophile a mixed color.

[*Leishman's Method.*—Leishman[1] has described a modification as follows: Two solutions are first prepared and then mixed. Solution A is a 1 per cent. solution of medicinal methylene-blue (Grübler) in distilled water. It is rendered alkaline by the addition of 0.5 per cent. of sodium carbonate and is then heated at 65° C. for twelve hours, and finally allowed to stand at room temperature for ten days before it is used. The second solution is a 0.1 per cent. solution of eosin (Extra B. A., Grübler) in distilled water. Equal volumes of these solutions are mixed in a large open vessel and allowed to stand for from six to twelve hours, being stirred from time to time with a glass rod. The precipitate is collected on filter-paper and washed with distilled water until the washings are nearly colorless. The residue is collected and is dissolved in methyl alcohol in a proportion of 0.15 per cent.

Method of Staining.—Cover-glass preparations without fixation are covered with 3 or 4 drops of the stain, to which after half a minute

[1] *Brit. Med. Jour.*, Sept. 21, 1901.

twice as much distilled water is added. The diluted stain is allowed to act for five or ten minutes, then washed in distilled water, and a few drops of the water are allowed to rest on the smear for one minute longer.

Wright's Method.—Recently Wright has considerably improved Leishman's stain. The advantage of Wright's method consists in the rapidity of preparation of the stain and the accuracy of the result. For details the reader must be referred to Mallory and Wright's *Pathologic Technic.*

Jenner's method has become a favorite one, and gives very satisfactory results. A 1.2 to 1.25 per cent. watery solution of Grübler's yellow water-soluble eosin and a 1 per cent. watery solution of Grübler's medicinal methylene-blue are mixed in a basin, stirred, and allowed to stand twenty-four hours. The mixture is filtered and the sediment dried at 55° C., after which the powdered filtrate is washed with distilled water, filtered, and again dried. A 0.5 per cent. solution of this powder in pure methyl alcohol constitutes the staining fluid. Films of blood are stained, without previous fixation, for from one to three minutes and washed with distilled water a few moments until of a pink color.—Ed.]

Before proceeding to the study of the histology of the blood, two important methods must be described for which the dry preparation can be directly employed without previous fixation: 1. The demonstration of glycogen in the blood; 2. The microscopic demonstration of the distribution of alkali in the blood.

Demonstration of Glycogen in the Blood.—This can be done in two ways. The original procedure, as recommended by Ehrlich, was to treat the preparation, while under the microscope, with a drop of thick clear iodin-gum solution; but the following method is better: The preparation is placed in a closed vessel containing crystals of iodin, where it assumes within a few minutes a dark-brown color; it is then imbedded in a saturated solution of levulose, which, as is well known, possesses a high index of refraction. In order to preserve the preparation it is necessary to surround the cover-glass with cement.

By both methods the red-blood-corpuscles are rendered conspicuous by the iodin stain, and show no morphologic change. The white blood-corpuscles are but feebly stained except the parts containing glycogen, and no matter whether the glycogen is within white blood-corpuscles or extracellular in products of decomposition, these are characterized by a beautiful mahogany-brown color. The second method is especially to be recommended on account of the strong clearing action of the levulose syrup, because with the employment of the iodin-gum

solution a small amount of glycogen may escape observation owing to the opaqueness of the gum or its own peculiar staining. This second method of examination is therefore recommended in cases of diabetes and other diseases.[1]

Microscopic Demonstration of the Distribution of Alkali in the Blood.—This method is based on a procedure elaborated by Mylius for the demonstration of alkali in glass. Iodin-eosin makes a combination readily soluble in water with a red color, but insoluble in ether, chloroform, and toluol. In contrast to this, the free acid stain as it is made from the salt by acidifying the solution is very insoluble in water, but readily soluble in organic solutions, so that on shaking it dissolves completely in the ethereal solution with the production of a yellow color. If this is allowed to fall on glass on which there is an alkaline precipitate from decomposition of the glass, this precipitate becomes conspicuous by a beautiful red color on account of the formation of an intensely colored salt.

In employing the test on blood, all vessels used in the staining, as well as the cover-glasses, must naturally be cleansed by acids of possible alkaline precipitates. Immediately after making the dry preparation it is placed in a glass vessel containing chloroform or a chloroform-toluol solution of free iodin-eosin. In a short time it becomes a dark red. It is then quickly transferred to another vessel containing pure chloroform, which is changed once, and the preparation is then mounted, moist with the chloroform, in Canada balsam. The morphologic elements retain their shape unaltered. The plasma becomes an evident red and the red blood-corpuscles remain unstained. The protoplasm of the white blood-corpuscles is stained red; the nuclei are unstained and appear as vacuoles (negative staining). The fragmented corpuscles are intensely red, as likewise the fibrin. This stain is extremely instructive and shows many details not apparent by other methods, but of interest largely on account of the beauty of the pictures. It is especially valuable since it brings out conspicuously the artefacts of the dry preparation, and every technical error, acting as it were as a sort of control. This method is scientifically important in that it demonstrates the distribution of alkali in the individual elements of the blood. It appears that there is no free alkali reacting to iodin-eosin present in the nuclei. These therefore react as neutral or acid. The protoplasm of the leukocytes, on the contrary, is invariably alkaline, especially that of

[1] This method is likewise strongly recommended for the demonstration of glycogen in secretions—*e. g.*, gonorrheal pus invariably shows a considerable glycogen reaction of the pus-cells. It is also found in cells of tumors taken from the exudate or by scraping.

the lymphocytes. Especial attention may also be called to the marked alkalinity of the blood-platelet.

NORMAL AND PATHOLOGIC HISTOLOGY OF THE BLOOD.

THE RED BLOOD-CORPUSCLES.

In dry preparations properly prepared the red blood-corpuscles preserve their natural size and form, and show plainly their biconcavity. When isolated, they appear as round, homogeneous bodies about 7.5 μ diameter. They are stained most intensely at the thick peripheral part, and least at the center corresponding to the depression. The stains which have been described do not tint the stroma, but only the hemoglobin, so that the intensity of color acts as a criterion for the expert in estimating the amount of hemoglobin in the individual cells, and is a much more satisfactory criterion than the natural hemoglobin color seen in fresh preparations. [Weidenreich,[1] in an article on the structure and form of the red corpuscles, has come to the conclusion that the erythrocyte is not a biconcave disc, but is bell-shaped, and may swell to the form of a sphere from absorption of liquid or become converted into a flat disc by loss of water. He states that the so-called "shadow corpuscles" are simply the collapsed membrane of the corpuscle. Treating the preparation with chromic acid makes it possible to recognize a residuum of hemoglobin in the interior of these shadows. With regard to the intimate structure of the red corpuscles, Weidenreich concludes that there is no stroma, but simply a membrane containing a structureless liquid and yellow colored material. F. T. Lewis[2] has recently confirmed these views regarding the form of the mammalian red corpuscles.—ED.] Corpuscles poor in hemoglobin are readily recognized by their pale staining, and especially by the more pronounced size and transparency of the central zone. In more marked cases they may be characterized by the staining of the peripheral zone alone; these were appropriately designated by Litten as "pessary forms." The faint staining in these cases can not be attributed, as E. Grawitz assumes, to a lessened affinity of the hemoglobin for the dye. Such a qualitative metamorphosis in the hemoglobin, which causes it to behave differently to stains, is unknown even in anemic blood. When the blood-discs stain less evidently, therefore, this is attributable only to a lessened amount of hemoglobin.

[1] *Arch. f. mikroskop. Anat.*, 1902, lxi., 3, p. 459.
[2] *Jour. of Med. Research*, Jan., 1904.

Such a diminution in the amount of hemoglobin is seen in all anemic conditions (especially the post-hemorrhagic, secondary and chlorotic), except pernicious anemia, in which, as first pointed out by Laache, the individual discs show an increased amount of hemoglobin.

In order properly to understand the pathologic conditions, it must be remembered that the individual red blood-corpuscles are not exactly similar in normal blood. Even physiologically, cells are continually destroyed (used up) and replaced by new ones. Every drop of blood contains erythrocytes of very different ages. It is easy to understand therefore that injurious influences, when not too great, may affect individual red blood-corpuscles differently. Elements possessing the least power of resistance—*i. e.*, the oldest—succumb to the injury, while others are able to withstand it.

Among these moderately severe irritations we may undoubtedly place the condition of the blood itself in anemia, the effect of which can be studied in cases of acute post-hemorrhagic anemia.

In all anemic conditions characteristic changes are observed in the blood-discs.

Anemic or Polychromatophilic Degeneration of the Red Blood-corpuscles.—This change, first described by Ehrlich, later by Gabritschewski, who bestowed on it the second name, is seen exclusively in stained preparations. It consists in the red blood-discs taking on a mixed instead of the normal hemoglobin color. In preparations of normal blood stained with hematoxylin-eosin, for instance, the red blood-corpuscles are pure red. In preparations of blood from chronic anemia, in which all degrees of fragmentary degeneration occur, they may show a delicate violet or blue-red, or even an intense blue, with scarcely a trace of red. Such corpuscles are easily recognized by their peculiar fragmented margins as dying elements.

Ehrlich suggested the theory that this behavior toward stains indicates the gradual death of the red blood-corpuscles, especially of the older forms, by a process of coagulation-necrosis of the discoplasm. This becomes laden, as in coagulation-necrosis generally, with the albumin of the blood, and thereby becomes capable of taking up nuclear stains. At the same time the discoplasm loses its power of holding the hemoglobin, and, in accordance with the degree of the alterations, gradually yields it to the blood-plasma, the disc in the meantime losing more and more the specific hemoglobin stain.

This view was opposed from different sides, first by Gabritschewski, later by Askanazy, Dunin, and others, who insisted that the polychromatophilic discs were not dying forms, but, on the contrary, young

forms. This opinion was based on the fact that in certain anemias the primary stages of the nucleated red blood-corpuscles are often polychromatic.

On account of its theoretic importance the evidence which upholds the degenerative character of these forms is detailed briefly:

1. The appearance of the erythrocytes which show the highest grades of polychromatophilia. By the breaking up of their margins they appear to every eye practised in the study of morphologic conditions as evident degeneration-forms in the act of solution.

2. The fact that such changes can be produced experimentally in considerable numbers in the blood of animals, for instance, by inanition; in other words, by conditions in which there can be little question of a new formation of red blood-corpuscles.

3. The clinical experience that after acute losses of blood in man these anomalies of staining are observed in numerous cells within the first twenty-four hours, while according to careful examinations of several hundred patients no nucleated red blood-corpuscles are to be found during this period.[1]

4. Nucleated red blood-corpuscles, especially megaloblasts, frequently show polychromatophilic degeneration. This fact is so evident that it can scarcely escape the observation of the inexperienced. Ehrlich is well known to have been the first to call attention to this condition. Moreover, it was the types of normal regeneration, the normoblasts, which were usually free from polychromatophilic degeneration even in animals which furnished the grounds for its discovery. Askanazy declares that he found polychromatophilia in all the nucleated red blood-corpuscles of the bone-morrow in one case of empyema immediately after resection of the ribs, but this is probably attributable to peculiarities of this case or to the uncertainty of the staining method employed, namely, eosin-methylene-blue, which must be considered as very inappropriate, inasmuch as overstaining with the blue readily occurs. (The authors especially advise for the study of anemic degeneration the triacid solution or the hematoxylin-eosin mixture.)

From what has been said, and from the recent work of Pappenheim and Maragliano, the authors hold that polychromatophilia is a sign of degeneration in the affected cells. The occurrence of such altered erythroblasts must, therefore, be referred to severe injuries of the blood,

[1] Though in opposition, Dunin asserts that the occurrence of nucleated red blood-corpuscles within the first twenty-four hours after the loss of blood, is the rule, the authors still insist that such an assertion is not consonant with actual facts; though they will admit that a single case might show such a rarity.

on account of which they are abnormal when produced. A sufficient number of analogies for this can be found in general pathology.

[Türk[1] expresses it as his view of polychromatophilia that the basophilia is connected with the poverty in hemoglobin, since the normal oxyphilia of the hemoglobin conceals the basophilia of the stroma. He does not believe that the phenomenon is in any sense degenerative, but rather one connected with the immature condition of the red corpuscle. At the same time he believes there is an abnormal condition of these cells, and in short the condition is one of anomaly rather than of degeneration or immaturity.

In this same connection the editor wishes to refer to his own experience in the matter, and to quote from an article "on the Pathology of the Erythrocyte."[2]

"I may confirm some of these observations from my own experience. I have found that the corpuscles poor in hemoglobin are more apt to present irregularity in the matter of receiving color, and have frequently found that this was most marked in the center of the corpuscle; moreover, in a case of pernicious anemia in which the bone-marrow was red, I found an enormous proportion of polychromatophilic cells in the bone-marrow. This affected not only the adult cells, but the youngest nucleated forms as well. . . . Maragliano and Castellino, in their studies of necrobiosis, found that the endoglobular areas of decolorization invariably received basic stains; and other observers, like Heinz and Browicz, found that fragmented corpuscles behaved somewhat similarly."—ED.]

A second alteration found in the red blood-corpuscles in anemia, is **poikilocytosis.** This consists in the appearance of more or less numerous larger, smaller, and very small red elements. Laache first drew attention to cells larger than normal in Biermer's anemia, and his finding has since then been confirmed; yet in all other anemias of severe or moderately severe character the red blood-corpuscles show a diminution in size and in the amount of hemoglobin. This contradiction, which was first noted by Laache, but which could not be explained, has been satisfactorily cleared up by Ehrlich's investigation of the nucleated primary stages of the megalocytes and the normocytes (see below). [Poikilocytes were first described by Damon, of Boston, in a paper on leukemia published in 1864.—ED.]

The blood-picture of anemia is made more variegated by the appearance of smaller cells of abnormal, irregular shape, simulating pears, air

[1] *Vorlesungen Ueber klin. Hematol.*, 1904.

[2] *Contributions from the William Pepper Laboratory of Clinical Medicine*, 1900.

balloons, and small boats. Still in well-prepared dry specimens the central biconcavity is usually evident in the smallest forms, with the exception of the so-called "microcytes." These are small spherical forms to which in the first period of microscopic hematology special significance was attributed in the diagnosis of severe anemias, though they are nothing more than contracted forms of the poikilocytes; or, in other words, show the same relation to the poikilocytes as the thorn-apple forms to the normal red blood-corpuscles. We find microcytes, therefore, but rarely in dry preparations, and much more frequently after long observation of moist ones.

It is further important to know that the poikilocytes may show a certain amount of movement in fresh blood, which has given rise to frequent error; for instance, at the beginning of the microscopic study of the blood they were considered to be the excitants of malaria; and somewhat larger forms were recently pointed out by Klebs and Perles as amebæ. With Hayem, therefore, who described these forms from the first as pseudoparasites, the author must warn against attributing to them a parasitic character.

The origin of poikilocytosis, previously much discussed, is now commonly explained according to Ehrlich's hypothesis. On account of the fact that it is possible to produce poikilocytosis experimentally by careful heating, we are forced to the conclusion that poikilocytes are products of fragmentation of the red blood-corpuscles ("Schistocytes," Ehrlich). This theory accords with the fact that even the smallest fragments show in dry preparations the biconcave form. For, containing as they do the specific protoplasm of the blood-discs, the discoplasm, "the tendency is natural to assume the typical biconcave form in a condition of rest."

Other qualitative alterations of the protoplasm of the poikilocytes are not perceptible on staining. Full functionary powers can therefore be assumed for them. Consequently their origin may be considered as a compensatory reaction to the decrease in the number of corpuscles, since by the breaking up of a large corpuscle into a number of small ones the respiratory surface is decidedly increased.

Nucleated Red Blood-corpuscles.—A third morphologic abnormality, ordinarily seen in severe grades of anemia, is the appearance of nucleated red blood-corpuscles.

Without going too much into detail in regard to the origin of the blood elements, the present teaching in relation to the nucleated red blood-corpuscles must be mentioned.

Since the fundamental work of Neumann and Bizzozero, nucleated

red blood-corpuscles have been generally recognized as normal young forms; while Hayem's theory, which insists on the origin of the erythrocytes from the blood-platelet, has been allowed to fall into the background, except by the author himself and his pupils.

Ehrlich drew attention to the clinical significance of the nucleated red blood-corpuscles in the year 1880, when he demonstrated in so-called secondary anemias and in leukemia nucleated erythrocytes of normal size—"normoblasts"; and in Biermer's anemia over-sized elements—"megaloblasts" or "gigantoblasts." He showed also at the same time that the megaloblasts played a prominent role in the formation of blood in the embryo. In 1883 Hayem made a corresponding division of the nucleated red blood-corpuscles, namely: (1) "globules nuclées géantes," which he found exclusively in the embryo; (2) "globules nuclées de taille moyenne," which were invariably present in the later stages of embryonal life and in adults. In 1890 W. H. Howell likewise found in the embryos of cats two varieties: (1) very large erothrocytes resembling the blood-cells of reptiles and amphibia ("ancestor corpuscles"); and (2) others resembling those ordinarily found in mammalia. Recent investigators, as H. F. Müller, C. S. Engel, Pappenheim, and others, have also preserved this division of hematoblasts into normoblasts and megaloblasts. Moreover, it has been generally recognized that the normoblasts occur in the bone-marrow of adults as the primary stages of the non-nucleated erythrocytes, while the megaloblasts are never found there normally, except in the embryo and in the first years of extra-uterine life.

Still, S. Askanazy has expressed the view that normoblasts may be derived from megaloblasts, and he consequently denies any particular difference. Schaumau, too, considers the separation into two varieties as not absolutely certain, because it is sometimes difficult to say whether certain cells belong among the normoblasts or megaloblasts.

The authors differentiate three varieties of nucleated red blood-corpuscles on the ground of their following properties:

Normoblasts.—These are red blood-corpuscles of normal size, characterized by a nucleus,—sometimes even two to four nuclei,—and a protoplasm which shows as a rule a pure hemoglobin color. Ordinarily the sharply circumscribed nucleus is situated concenrically, takes up the greater part of the cell, and is striking on account of its intense staining, which far surpasses that of the nuclei of the leukocytes, and, as a matter of fact, of all known nuclei. This peculiarity is so characteristic that free nuclei, such as are sometimes found in anemia and frequently in leukemia, are readily recognized as the nuclei of normoblasts.

Megaloblasts.—These are two to four times larger than the normal red blood-corpuscles. Their hemoglobin, which constitutes the greater part of the cell, very frequently shows more or less anemic degeneration. The nucleus is larger than that of the normoblasts, but takes up a comparatively smaller part of the cell. It is irregular in shape and its margin is frequently indefinite; but it is especially differentiated from the nucleus of the normoblasts by a much less marked affinity for the nuclear stains,—in fact, this affinity is sometimes so slight that the inexpert may fail to notice the nucleus.

We sometimes see cells belonging to this category of such immense size as to deserve the name gigantoblasts; still these are in no other way separable from the ordinary megaloblasts.

It can not be denied that it is often difficult to decide whether a definite cell should be considered a particularly small megaloblast or a large normoblast. In such cases it is well to overhaul the specimen for pronounced hematoblast-forms, free nuclei, or megalocytes, in order to obtain indirectly evidence in regard to the doubtful cells.

Microblasts.—These are seen occasionally in traumatic and other anemias; yet so far have attracted no particular attention on the part of investigators.

The question of the significance of *normoblasts* and *megaloblasts* has been the cause of lively discussion, which brought forth good reasons for and against the differentiation of these two cell-forms. Looking over the material at hand, one is forced to separate megaloblasts and normoblasts on account of the further fate and peculiarities of their nuclei on the one hand, and because of the result of clinical observation on the other.

The Fate of the Nucleus.—As to the mode of transformation of nucleated erythroblasts to non-nucleated erythrocytes, two almost diametrically opposite views have been in vogue for some time. The chief advocate of the first, Rindfleisch, taught that the erythroblast was transferred to an erythrocyte by the outwandering of the nucleus, and that this, by the aid of the small amount of protoplasm adhering to it, took up new substance from the surrounding plasma, imbibed hemoglobin, and became again a new erythroblast. This doctrine stands in direct opposition to the other, according to which the erythroblasts are transformed to non-nucleated discs by the destruction and solution of the nuclei within their own bodies ("karyorrhexis, karyolysis"). The writers who advocated this view in numerous publications and described it as the exclusive method of erythrocyte formation, are Kölliker and E. Neumann.

Rindfleisch based his theory on processes which he observed directly in the blood of guinea-pig embryos and in teased preparations of bone-marrow in physiologic salt solution.

E. Neumann considers Rindfleisch's position as untenable, because his observations were made only after injury of the blood by the salt solution and by the teasing. He contends that if the preparation is so made that every chemic and mechanical injury to the blood is avoided, the emergence of the nucleus as described by Rindfleisch does not occur.

The Kölliker-Neumann view, that the nucleus gradually meets its fate within the cell itself, is supported not by observation of the process, but by the fact that in suitable selected cases—*e. g.*, in fetal bone-marrow, hepatic blood, and in leukemia—all phases of nuclear metamorphosis in the transition of erythroblasts to erythrocytes are found. Moreover, v. Recklinghausen claims that he observed this solution of the nucleus within the cell in rabbits' blood which he preserved in a moist chamber. Pappenheim's suggestion, however, that we have to do in these cases with a process similar to that described by Maragliano and Castellino as artificial necrobisosis, appears worthy of mention.

As is the case with the views in regard to the formation of erythrocytes, there is a wide divergence in the theories adduced to explain the significance of the "free" nuclei observed in numerous cases. Kölliker taught that these nuclei are never free from protoplasm, but are invariably surrounded by a very small margin; Rindfleisch considers that they have escaped or were thrown off from the erythroblasts; and Neumann believes them to be young forms of erythroblasts.

Ehrlich was the first to endeavor to bring these opposite views of Rindfleisch's and Neumann's into agreement. He taught that both varieties of transformation occurred. In blood preparations containing a large number of normoblasts—*e. g.*, in "blood crises" (see below), or leukemia—an uninterrupted series of pictures may be found showing the nuclei of the erythroblasts leaving the cells in order to become free. Moreover, these forms are found even in preparations where every pressure on the specimen has been avoided. On the other hand, no matter how rich the blood may be in normoblasts, Neumann's metamorphosis of the nucleus is practically never observed. It is quite different in the case of megaloblasts. Among these we find but few examples in which traces of destruction or solution of the nucleus is not evident, and in a specimen of Biermer's anemia containing a reasonably large number of megaloblasts it is possible to follow Neumann's process in an uninterrupted series from megaloblasts with intact nuclei

through all stages of karyorrhexis and karyolysis to the megalocyte.[1] [Some recent studies of the basophilic granules of nucleated corpuscles (normoblasts as well as megaloblasts) suggest that these structures may be the result of nuclear degeneration.—ED.]

From Ehrlich's findings, therefore, it appears that normoblasts become normocytes by the wandering out or the throwing off the nucleus; megaloblasts, megalocytes by destruction of the nucleus within the cell.

Moreover, M. B. Schmidt, without reference to Ehrlich's observations, assumes after investigation of bone-marrow sections of extra-uterine animals that erythrocytes are formed in both ways.

Recently Pappenheim, partly in coöperation with O. Israel, devoted special attention to this subject in a series of investigations on the embryonal blood of mice. Like Rindfleisch, he was able to produce the outwandering of the nucleus by the addition of physiologic salt solution to fresh blood, and he considers that at least in the embryonal blood the outwandering of the nucleus occurs only artificially. The transformation to erythrocytes in embryonal blood takes place exclusively by the destruction and solution of the nucleus within the cell, and it is indifferent whether the cells be megaloblast or gigantoblasts, or cells of normal size. Contrary to Rindfleisch and Neumann, he regards the free nucleus, not as a beginning stage of development, but as the eventual remnant of the degenerated dying blood-cell which has been brought to this condition by a solution of the protoplasm ("plasmolysis"). Clinical observations of diseased blood fail to support this view, inasmuch as even in suitable cases with numerous free nuclei (leukemia, blood crises) no transition-forms are found. In describing such a case of leukemia, Pappenheim himself confesses that the occurrence of free nuclei could be explained in this instance by their outwandering.

Although Pappenheim recognizes no difference in regard to the fate of the nucleus in megaloblasts and normoblasts in embryonal blood, he considers Ehrlich's separation of the erythroblasts into these two groups—that is, into two hematogenetically different species of cells—as undoubtedly correct. He refuses only to see differential characteristics in the size of and amount of hemoglobin in the cells; and though he acknowledges that these differences were generally evident in normoblasts and megaloblasts, he contends they were subject to many irregularities which under the circumstances made the classification of an indi-

[1] The punctate and granular-like deposits stained by methylene-blue, and found by Askanazy and A. Lazarus in the red blood-corpuscles in numerous cases of pernicious anemia, are probably products of such a nuclear destruction.

vidual cell very difficult. The principal feature in the differentiation is furnished by the character of the nucleus (a fact which Ehrlich has always insisted on). The nuclei of undoubted normoblasts are characterized by their lack of structure, their sharp limitation, and their intense affinity for the nuclear stains, properties which in histology (Pfitzner) are comprehended by the name *pyknosis* and are considered as signs of age. The nuclei of the megaloblasts are irregular, show well-developed structure, and stain much less intensely.

Clinical Differences.—Normoblasts are found almost regularly in all severe anemias following trauma, inanition, or organic disease. They are usually scanty in number, so that a long search is necessary to find them, though sometimes, usually in acute, but also in chronic anemias, even in cachectic conditions, one or more normoblasts may be found in every field.

v. Noorden was the first to describe a case in which normoblasts occurred transiently in the circulating blood in such immense numbers during the course of hemorrhagic anemia that the microscopic picture (a marked hyperleukocytosis existing at the same time) almost resembled that of a myelogenic leukemia. Since in this case there was almost a doubling of the red blood-corpuscles, v. Noorden designated the condition by the name "blood crisis."

For an accurate determination of a blood crisis the following procedure is recommended:

1. Estimation of the absolute number of red blood-corpuscles.
2. Estimation of the ratio of the white blood-corpuscles to the red.
3. Estimation of the ratio of the nucleated reds to the whites in a dry preparation, by means of the square ocular blend (see page 20).

If we find, for instance, in a case of anemia 3,500,000 red blood-corpuscles, the relation of the whites to the reds=1 : 100, and that of the nucleated reds to the whites=1 : 10, there would be in a cubic millimeter 2500 nucleated reds or 1000 erythrocytes to 1 erythroblast.

The megaloblasts, on the contrary, are never found in traumatic anemia. Moreover, in chronic anemias of the severest grades, as, for instance, from a long-continued syphilis, carcinoma ventriculi, etc., they are usually sought in vain, while they are occasionally found in leukemia. Nevertheless, much milder conditions apparently, in which the anamnesis, etiology, and general objective symptomatology point to an essential progressive anemia, are almost without exception characterized by their occurrence in the blood. In late stages of the disease, however, they are more scanty, and it often requires a long search over one or several preparations to find them. From this the rule is evident that the examination of a case of a severe anemia should never be

considered complete until at least three or four preparations have been carefully gone over with the aid of an oil-immersion lens.

[A number of authors have discussed the difficulty of differentiating normoblasts and megaloblasts when certain apparently intermediate types are present, and this may explain the difference in opinion regarding the occurrence of megaloblasts in secondary anemias. Undoubtedly these cells occur in lead-poisoning with considerable frequency, and quite often in cancerous and other secondary anemias. It may be doubted, therefore, if the view regarding the rarity of the occurrence will be generally accepted.—ED.]

This clinical differentiation of the two forms of hematoblasts leaves only one question untouched, namely, whether megaloblasts or normoblasts can become transformed the one into the other. We find normoblasts in all cases of anemia in which a normal type of regeneration takes place only more energetically than under ordinary circumstances. Almost all anemias with known causes, namely, acute hemorrhages, chronic hemorrhages, impoverishment of blood by inanition, cachexias, blood intoxications, hemoglobinemia, etc.,—in short, all conditions which are ordinarily included under the names secondary or symptomatic anemia may show this increase of normal blood formation. In the condition which Biermer, on the basis of its clinical peculiarities, designated "essential pernicious anemia," we find, however, megaloblasts the representatives of an embryonal type of development. How much they participate in the formation of blood in pernicious anemia is evident from the fact that in all cases of pernicious anemia, as was demonstrated by Laache, megalocytes are present, and in some cases they represent the predominant erythrocyte. While in simple anemia, therefore, there is a tendency for the red blood-corpuscles to occur in small forms, in pernicious anemia, and in it exclusively, we find the opposite tendency. This constant difference can not be the result of accident, but must depend on rule; in other words, oversized blood-corpuscles must be produced by pernicious anemia. This was logically proved by Ehrlich's demonstration of megaloblasts. All attempts to obliterate the difference, or to deny that any exists between megaloblasts and normoblasts, are frustrated by the undoubted clinical fact that the blood of pernicious anemia is megalocytic.

The occurrence of megaloblasts and megalocytes is therefore a proof that the regeneration of the blood in the bone-marrow is not taking place normally, but in a way approaching the embryonal type. Extreme cases like that of Rindfleisch's, in which the entire bone-marrow is filled with megaloblasts, are naturally rare. It is sufficiently diag-

nostic of the pernicious character "when not the entire bone-marrow, but only a considerable part is in the process of megaloblastic degeneration."[1]

Moreover, we are in a position to state that the megaloblastic transformation represents a highly unprofitable process, and for the following reasons: 1. Because the new formation of red blood-corpuscles of megaloblastic type is a much slower process. This is proved particularly by the fact that megaloblasts always occur in small numbers, while normoblasts, as previously mentioned, are frequently very numerous. Accordingly "blood crises" are not observed in megaloblastic anemias. 2. Because the megalocytes arising from the megaloblasts offer a relatively small surface for respiration in comparison to their volume, and therefore constitute a type the reverse of useful for anemic conditions. This is the more evident when it is recalled that the formation of poikilocytes is a compensatory process.

The megaloblastic degeneration of the bone-marrow is apparently to be referred to chemic influences which have the power thus to change the regeneration type. In the majority of cases the excitant is not known, and the process is therefore fatal because the means of terminating it are not known. This is not contradicted by the fact that bothriocephalus anemia, as is well known, generally offers a good prognosis because, although of megaloblastic type, its cause is known and can be removed. As in many infectious diseases, different individuals react to the bothriocephalus very differently. Some show no symptoms; others, the symptoms of a simple anemia, possibly with normoblasts; while a third group present the typical picture of pernicious anemia, which for many years, as long as its etiology remained unknown, could not be differentiated from Biermer's disease. It can not be wrong, therefore, to designate a severe bothriocephalus anemia as a pernicious anemia with a known removable cause. This position is very convincingly supported by a case of Askanazy's, which showed a severe pernicious anemia with typical megaloblasts, and in which, after removal of the bothriocephalus, the megaloblastic character of the blood quickly disappeared and was replaced by a normoblastic condition that rapidly eventuated in complete recovery. This observation is so significant that it is surprising how Askanazy can believe that a transition between megaloblasts and normoblasts takes place, when this case clearly and evidently shows that

[1] It appears not superfluous to add that what has been said in regard to the diagnostic significance of megaloblasts refers only to the blood of adults. The appearances of children's blood, which frequently deviates from that of adults, will be studied in the special part (Anæmia Pseudoleukæmica Infantum).

megaloblasts are manufactured only under the influence of a specific intoxication. If we knew the toxic agents and were able to remove them, it is *a priori* certain that—in not too advanced stages of pernicious anemia—the bone-marrow would again take on its normal normoblastic type of regeneration. In more than one case clinical observation supports this view. For instance, it is by no means a rarity to see an apparent recovery from a megaloblastic anemia, which recurs, however, after a longer or shorter period, to lead eventually to death. These cases absolutely demonstrate that the megaloblastic degeneration can retrogress, and that in individual cases this result may be brought about by arsenic treatment. Still, a definite cure is not obtained under these circumstances, because we do not know the etiologic agent, and hence have no methods of overcoming it. The megaloblastic anemias therefore, apart from the group of bothriocephalus anemias, offer a bad prognosis.

Basophilic Granulations of the Erythrocyte.—This condition may be properly considered in this place on account of its possible relation to polychromatophilia, and of its bearing on the fate of the nucleus of the hematoblast. Askanazy (1893) first described such granules in the nucleated red corpuscles of pernicious anemia. Schaumann (1894) found similar formations in bothriocephalus anemia, and Lazarus (1896) identified them in a series of cases of pernicious anemia, but failed to find them in other conditions. A large number of investigators have since investigated the subject, and the granules have been found in various secondary and primary anemias, as well as in apparently normal cases. Stengel, White, and Pepper examined the blood of 105 medical and surgical cases, and found the granules in 34 representing a wide range of pathologic conditions. In addition they found them in 11 of 18 cases of chlorosis; in 7 of pernicious anemia, in 10 of leukemia, and in a considerable number of cases of lead-poisoning. Their relation to the last condition was first indicated by Behrendt and Hamel, and has been confirmed by a number of clinicians.

Considerable discussion has arisen regarding the nature of these granules. Askanazy first suggested that they are nuclear products resulting from karyorrhexis, a view which has been adopted by a number of investigators. Grawitz, however, insists that they are derived from a degeneration of the cytoplasm, and is supported in this view by several recent authors. It must, the writers confess, be admitted that the weight of evidence is rather in favor of the nuclear origin, though his own studies had led him to adopt the view of Grawitz. The subject, however, is still unsettled. Among the recent

contributions an important one is that of Schmidt,[1] who concludes that the granules are not always of the same nature, being sometimes regenerative, and in other cases the results of degeneration of the nucleus. He does not believe there is any evidence in favor of their origin from degenerations of the protoplasm. Some have referred to the intact character of the nuclear outline as an evidence that nuclear degeneration has played no part in the formation of the granulations, but Schmidt believes this view incorrect, as the separation of the granules may form in the stage of development of the nucleus before its sharply outlined form has been assumed. Schmidt does not believe that there is any special function attaching to these granular bodies. They seem to him to belong in general, however, in the same class with polychromatophilic cells and nucleated red corpuscles.

The occurrence of granules in mitotic nucleated cells (Bloch, Lazarus, Stengel, White, and Pepper) must be regarded as evidence of some value in contravention of the view that they result from karyorrhexis. Maximow suggests that the red corpuscle contains diffuse nuclear material from which the granules may arise without karyorrhexis. Ewing states that he has seen many transition-forms between fragmentation of the nuclei of megaloblasts and fine subdivision of these nuclei. It seems probable, as Grawitz, Schmidt, and some others have suggested, that there may be different forms of basic granulation of possibly varying origin.

Jawein[2] believes that the basophile granules occur only in young red cells, and are an evidence of regeneration. He thinks the view of Grawitz, that blood poisons can cause these cells, is very improbable. The fact that the granules occur with intact nuclei does not disprove karyolysis, as he has seen a red cell with two nuclei, one normal and the other undergoing solution.

White and Pepper[3] examined the blood in cases of chronic lead-poisoning as well as in workmen in lead-works, presenting no subjective symptoms; also the blood of persons subjected to excessive local or general applications of external heat, and that of men and animals subjected to experimental intoxication. In 4 cases of lead-poisoning the granules were invariably present and usually conspicuous. Of the lead-workers without subjective symptoms, there were 21 cases, in all of which granules were found. These workmen were from all parts of the

[1] *Experimentelle Beiträge zur Pathologie des Blutes.* Jena, 1902, Gustav Fischer, pp. 42, 4 lithogr. illustrations.

[2] *Berlin. klin. Wochenschr.*, 1901, No. 35.

[3] *Amer. Jour. Med. Sci.*, and *Trans. Assoc. Amer. Physicians*, 1901.

establishment, some being exposed to dust, others not so. In 2 cases the men had worked only four days in the works. Associated blood-changes were as follows: 12 showed slight poikilocytosis, 2 had deficient hemoglobin, 3 slight polychromatophilia, 5 showed normoblasts. In the experimental study it was shown that the granules could be made to appear in the blood twenty-four hours after the administration of lead acetate. One of the authors (Pepper) administered 7½ grains of lead acetate to himself, and found the granules in his blood within twenty-five hours. The blood from the portal and splenic veins in one of the dogs killed for the purpose showed more granules than the blood from the heart or mesenteric vessels, or that taken from the ear before death. In 5 later cases this difference of distribution could not be established. The granular cells could not be found in special abundance in the bone-marrow. They conclude that the granules represent a degeneration of the red corpuscles, and have no relation to nuclear fragmentation or polychromatophilia.

Reitter,[1] in studying the blood of 20 cases of advanced pulmonary tuberculosis, was able to demonstrate granular erythrocytes in every case, and indeed in every preparation. He was also able to show these bodies in the blood of healthy individuals, and concluded that the abundant presence of such formations alone constitutes a pathologic condition. The occurrence in normal persons has also been observed by others, namely, Askanazy,[2] Schaumann,[3] Lazarus,[4] Stengel, White and Pepper,[5] Grawitz,[6] Black,[7] Maximow,[8] Ewing,[9] Behrendt and Hamel,[10] White and Pepper.[11]

[R. C. Cabot[12] has described as "ring bodies (nuclear remnants?)" certain circular or figure-of-8 formations in the red corpuscles in cases of lead-poisoning, pernicious anemia, and other conditions in which nucleated red corpuscles were present. The ring-like body is composed of a set of dots or granules arranged as a circle or figure-of-8, staining *red* with Wright's modification of Leishmann's stain, and often showing a large dot at one point of the ring. He believes it probable that these formations represent nuclear remains.—Ed.]

[1] *Wien. klin. Wochenschr.*, 1902, xv., 47.
[2] *Zeitschr. f. klin. Med.*, Bd. xxiii.
[3] *Bothriocephalus Anemia*, Berlin, 1894.
[4] *Deutsch. med. Wochenschr.*, 1896, No. 23.
[5] *Amer. Jour. Med. Sci.*, May, 1902.
[6] *Deutsch. med. Wochenschr.*, Sept. 7, 1899; *Berlin. klin. Wochenschr.*, 1900, p. 181; *Amer. Jour. Med. Sci.*, Sept., 1900.
[7] *Deutsch. med. Wochenschr.*, 1899.
[8] *Archiv. f. Anat.*, 1899.
[9] *Clinical Pathology of the Blood*, 1803.
[10] *Deutsch. med. Wochenschr.*, 1899, No. 44.
[11] *Amer. Jour. Med. Sci.*, 1901.
[12] *Jour. Med. Research*, Feb., 1903.

THE WHITE BLOOD-CORPUSCLES.

The biologic significance of the white blood-corpuscles is so many sided that it indubitably represents the most interesting chapter in hematology. The knowledge that the white blood-corpuscles play an important rôle in the physiology and pathology of the human organism developed but slowly, for the reason that important functions were attributed with hesitancy to elements occurring in such relatively small numbers. A place in pathology was first assured to them by Virchow's discovery of leukemia. After Cohnheim's discovery that inflammation and suppuration were to be referred to the outwandering of white blood-corpuscles, the question of the function of the leukocytes became a burning one, and it was exactly such a discovery that was needed to throw light on the normal conditions. The fact that in diffuse inflammations large amounts of pus were frequently produced in a short time without impoverishment of the blood in leukocytes—in fact, even the opposite—provoked the conjecture that the source of the leukocytes must be exceedingly productive, and that their small number as compared with that of the red blood-corpuscles, was compensated for by a pre-eminent power of regeneration.

Subsequent to this a long time passed before the seed planted by Cohnheim bore its fruit in clinical histology. This was due to the fact that an accurate differentiation of the various leukocytes was extremely difficult by the methods of blood examination then in use. For although skilful investigators like Wharton Jones and Max. Schultze were able to recognize the different types of white blood-corpuscles, their knowledge did not reach the practitioner on account of the distinctions being much too subtle. Virchow himself, the discoverer of leukocytosis, attributed this condition to an increase in lymphocytes, when in fact only the polynulcear cells are usually concerned. Only after the differentiation was made simple by the aid of stained preparations did interest in the white blood-corpuscles progressively increase, as is proved by the extremely rich hematologic literature, especially on the subject of leukocytosis.

In spite of this recent advance a peculiar retrograde movement in the theory of leukocytes has been put on foot. Although after Virchow's description of the lymphocytes every effort was made to separate the different varieties of white blood-corpuscles from one another, and refer them when possible to their different sources, now every effort is directed toward placing all the leukocytes under one roof on the theory that the different forms are only different stages of development of the same cell.

The following sections will endeavor to show the untenableness of this theory.

NORMAL AND PATHOLOGIC HISTOLOGY OF THE WHITE BLOOD-CORPUSCLES.

Since Ehrlich's classification of the white corpuscles of normal blood of adult human beings has been accepted by the majority of writers, it is well to give a short description of them as observed in the dry, stained preparation.

1. **Lymphocytes.**—These are small cells, usually about the size of a normal red blood-corpuscle, with a large round, homogeneously

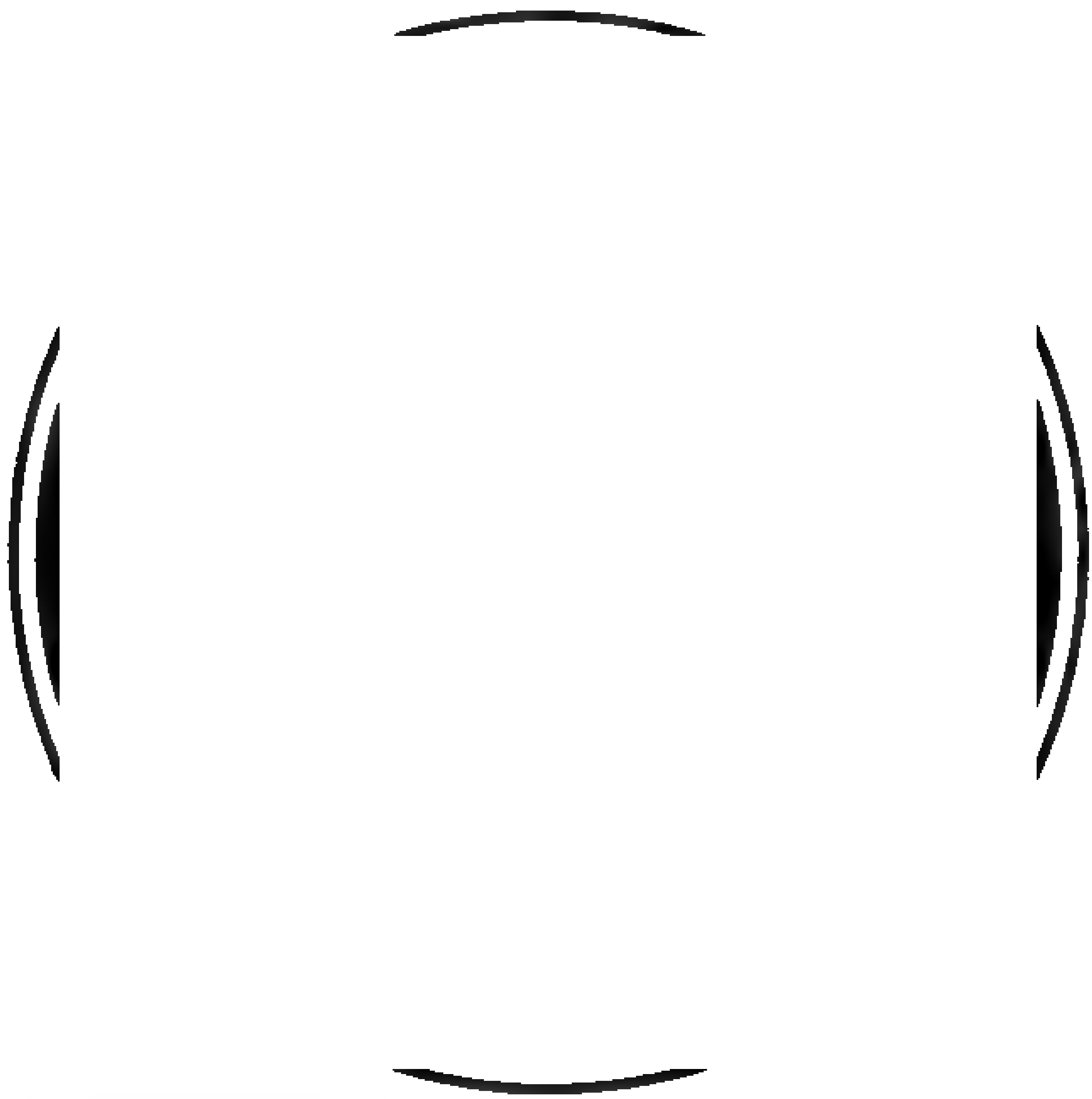

FIG. 1.—Filamentous appearance of the protoplasm at the margin of large lymphocytes; fragmented free plasma elements ("plasmolysis"). (After the photograph of a preparation of chronic lymphatic leukemia.)

stained nucleus situated concentrically and surrounded by a small margin of protoplasm. One frequently finds, especially in large forms, a small space between the nucleus and the protoplasm, very probably due to

artificial retraction. Nucleus and protoplasm are basophilic—in fact, the protoplasm shows a much greater affinity for many basic stains than the nucleus, so that on staining the latter appears as a relatively clear area in the midst of the intensely stained net-like protoplasm. Within the nucleus one or two nucleoli with a relatively thick deeply staining membrane are often recognized (Fig. 2). The protoplasm stained with methylene-blue and similar stains presents an irregular character, due, according to Ehrlich's first hypothesis, to a net-like structure rather than to granulation. The exterior contour of the lymphocytes, at least in the larger forms, is usually not quite smooth, but somewhat filamentous, dentate, or uneven (Fig. 1). Frequently, especially in the very

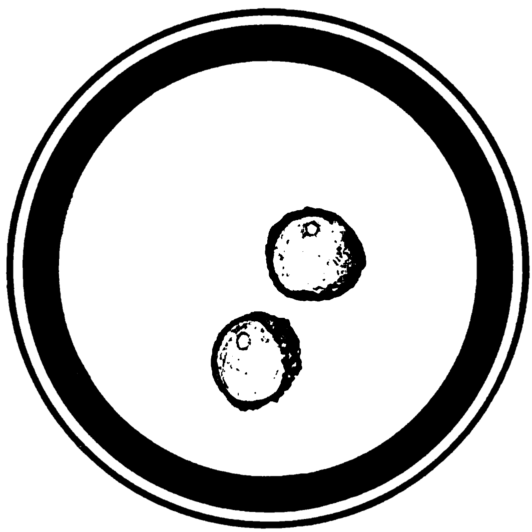

FIG. 2.—Nucleoli in large lymphocytes. (After the photograph of a preparation of chronic lymphatic leukemia.)

large forms, parts of the peripheral margin are broken off and are found free in the plasma. In stained preparations, particularly of lymphatic leukemia, these are readily recognized by their staining, which is exactly that of the protoplasm of the lymphocytes.

In the transformation of the nucleus a sharp indentation may occur even though rarely, and further metamorphoses as represented in the plate (Fig. 3, after Rieder), very different from those characteristic of the polynuclear cells.

The protoplasm shows no particular affinity for acid and neutral stains, and therefore, with triacid and hematoxylin solutions the small lymphocytes appear as feebly stained free nuclei. In the larger cells the protoplasm is likewise feebly stained by these solutions. The reac-

tion of the protoplasm as demonstrated by the iodin-eosin method, is markedly alkaline. It contains no glycogen.

All these properties taken together constitute a characteristic picture by which the lymphocytes can be recognized and differentiated from other cells even when fluctuations in size occur. As mentioned, they are ordinarily characterized by their smallness, their size being about that of the red blood-corpuscle. Yet in the blood of children under absolutely normal conditions larger forms, and in lymphatic leukemia very large forms, are found which the inexperienced have failed to recognize. For instance, Troje's "marrow cells," which even play a rôle

FIG. 8.—Nuclear transformation of lymphocytes. (Combined picture from a preparation of acute leukemia.) (From Rieder's *Atlas*.)

in the literature, have absolutely nothing to do with the bone-marrow, but are simply large lymphocytes, as has been proved by A. Fränkel.

In the normal blood of adults the number of lymphocytes amounts to about 22–25 per cent. of the colorless corpuscles.

An increase in the lymphocytes alone may occur, but is much rarer than an increase of other forms. When it does take place, it is designated by the specific name "lymphocytosis" or "lymphemia."

2. The **large mononuclear leukocytes** are to be strictly differentiated from the lymphocytes. These are cells two or three times the size of erythrocytes, with a large, oval, usually excentrically situated and feebly staining nucleus, and a relatively large amount of protoplasm.

The protoplasm is free from granulation, and is slightly basophilic, but in contrast to the protoplasm of the lymphocytes, less so than the nucleus. They are present in normal blood in small numbers (about 1 per cent.). Their whole appearance is different from that of the lymphocytes, and transitions between the two are not observed. In what blood-making organ they arise, whether spleen or bone-marrow, has not been determined, though many facts point to the latter as their place of origin.

These large mononuclear leukocytes are transformed within the blood to the following varieties:

3. **Transition-forms.**—These resemble in a general way the preceding, but are differentiated from them by a large indentation of the nucleus which frequently gives it the form of a wallet, by a somewhat greater affinity of the nucleus to nuclear dyes, and by the presence of a small number of neutrophile granulations in the protoplasm. This group and the last together constitute about 2–4 per cent. of all the white blood-corpuscles.[1]

4. **The (So-called) Polynuclear Leukocytes.**—Some of these arise, as will be discussed more thoroughly later, within the circulation from the transition-cells, though the greater part of them come into the circulation ready formed from the bone-marrow. These cells are somewhat smaller than those in groups 2 and 3, and are characterized by a peculiar polymorphous nucleus which shows a relatively long and irregularly indentated and contracted figure in the form of an S, Y, E, or Z. This nucleus may break up normally, even during life, into three or four small round individual nuclei, as was first pointed out by Ehrlich in a case of hemorrhagic small-pox, and is frequently seen in fresh exudates. This breaking up of the nucleus into several parts was previously noted as occurring under the action of several reagents, for instance, acetic acid; and on this account Ehrlich bestowed on the cell the not very appropriate name "polynuclear." Nevertheless, since this name has been accepted everywhere, and misunderstandings are not to be anticipated, it is better to preserve it, though it would be more exact to call them "polymorphonuclear cells."

The nucleus is deeply stained by all nuclear dyes; the protoplasm shows considerable affinity for the majority of acid stains, and is unmistakably characterized by numerous neutrophile granulations. The reaction of the protoplasm is alkaline, yet to a less degree than that of the lymphocytes. In the ordinary polynuclear cells no free glycogen

[1] In counting the blood-corpuscles groups 2 and 3 may be reckoned separately or together.

is present, yet in certain diseases cells are always found which give the iodin reaction.

Such cells containing glycogen were first demonstrated in diabetes (Ehrlich, Gabritschewsky, Livierato). The iodin reaction in white blood-corpuscles has been further observed in severe contusions and fractures two to three days after the trauma; in pneumonia, in rapidly progressing streptococcus and staphylococcus phlegmons, and after long-continued narcosis (Goldberger and Weiss). According to Ehrlich's view, the glycogen is not present in the cells as such, but in an unstainable combination, from which the glycogen is readily separated before giving the iodin reaction.[1] [Dunham[2] finds iodophilia in connection with suppuration that has not been walled off and is not of tuberculous character; also in pneumonia. Further, he found the condition also in leukemia, and cites the fact that Hofbauer found it in pernicious anemia, leukemia, and certain grave secondary anemias.

Locke and Cabot[3] recognize two types of iodophilia, one in which round or oval masses, 2μ to 8μ in diameter, are seen outside of the cells; and, second, an intracellular type, the granules being regular in shape and size, and occurring in the neutrophile cells. Occasionally, basophilic cells are affected. Their study of 432 cases led them to the conclusion that iodophilia is an indication of a general toxemia, such as may occur in a great variety of diseases, while most frequently coincident with the presence of pus. The test is by no means pathognomonic. They regard iodophilia as certainly indicative of a diseased condition, and among the disorders with which it is most regularly found are pyogenic infections, toxemia of bacterial origin, as in diphtheria, and typhoid fever, non-bacterial toxemia, such as uremia, disturbances of respiration, and grave anemias.—ED.]

We can not consider the "perinuclear" greenish granulations of the polynuclear cells described by Neusser as preformed elements (see p. 43).

The number of polynuclear leukocytes in the blood of a healthy adult amounts to about 70–72 per cent. of all the white blood-corpuscles (Einhorn).

5. **Eosinophile Cells.**—These are characterized by rough granulations which stain intensely with acid dyes; otherwise they resemble polynuclear neutrophiles.

When carefully stained, it is occasionally possible to see that the

[1] Czerny's assumption, that the cells that respond to the iodin reaction wander in from suppurative foci, is groundless and a simple examination of fresh inflammatory tissue is sufficient to show that the cells wandering out of the circulation already contain glycogen.

[2] *Boston Med. and Surg. Jour.*, June 1, 1901.

[3] *Jour. of Med. Research*, January, 1902.

periphery of the eosinophile granulations is more deeply stained than the interior. The nucleus is as a rule not so intensely stained as in the polynuclear neutrophiles, though its configuration is exactly similar. Both forms show also in common an active power of contractility by which they are able to emigrate from the vessels into exudates and pus. The size of the eosinophiles is frequently greater than that of the neutrophiles. Their number is normally about 2 to 4 per cent. of the whites.

6. **Mast-cells.**—Though in extremely small numbers, these are present in every normal blood; 0.5 per cent. of the whites may be considered their maximum. They are characterized by intensely basophilic granulations of very irregular size and unequal distribution. In addition the granulations show the peculiarity of not staining a pure color with the majority of basic dyes, but metachromatically, especially with thionin. This deviation from the color is, as Morgenroth discovered, even more marked on the employment of kresyl-violet-R (extra), when the granulations stain almost pure brown.

The staining power of the nucleus is very slight, and it is therefore difficult, without special staining methods, to pass judgment on its form. With the triacid mixture the granulations are unstained and the cells appear as clear, polynuclear cells free from granulations.

[Taylor[1] gives the following figures as the result of his personal observations: Total number of leukocytes, 3000 to 10,000; neutrophilic polymorphonuclear leukocytes, 55 to 80 per cent.; acidophilic polymorphonuclear leukocytes (eosinophiles), $\frac{1}{2}$ to 8 per cent.; non-granular mononuclear and transitional cells, 1 to 8 per cent.; acidophilic mononuclear cells, rarely seen; lymphocytes, 10 to 40 per cent.; mast-cells, very rarely seen.—ED.]

[The classification of Kanthack and Hardy is frequently adopted by English authors. This recognizes five types of cells: (1) Lymphocytes; (2) hyaline cells (large mononuclear cells of Ehrlich); (3) finely granular oxyphile cells (the neutrophile and amphophile cells); (4) coarsely granular oxyphile cells (eosinophiles); and (5) coarsely and finely granular basophiles (mast-cells).—ED.]

Pathologic Forms.—Under pathologic conditions are found not only alterations in the numbers of these cells, but also new forms not normally seen. To these belong:

1. **Mononuclear cells with neutrophile granulations** ("myelocytes," Ehrlich). These are usually very large with a relatively large faintly staining nucleus, which is frequently almost centrally located and

[1] "Studies in Leukemia:" *Contributions from the William Pepper Laboratory of Clinical Medicine*, 1900.

is uniformly surrounded by the protoplasm. The characteristic difference between them and the large mononuclear leukocytes of normal blood is that their protoplasm shows more or less numerous neutrophile granulations. Besides the large forms of myelocytes, there are others much smaller, almost approaching in size the erythrocytes; all grades of transition between these extremes are encountered.

In contrast to the polynuclear neutrophiles, they manifest on the warm stage no ameboid movement.

They constitute a regular characteristic of myelogenic leukemia, in which they occur in great numbers. Reinbach found them in one case of lymphosarcoma with metastasis to the marrow of the bone; A. Lazarus transiently in moderate numbers in one case of severe posthemorrhagic anemia; and M. Beck in one case of severe poisoning by mercury administered therapeutically. In addition, they are frequently found in diseases of children, especially anemia pseudoleukemica infantum; and K. Elze described them in a fifteen months old boy suffering from scrofula.

The occurrence of myelocytes in infectious diseases is of special interest. After Rieder had pointed out that myelocytes sometimes occur in acute inflammatory leukocytosis, C. S. Engel published the interesting observation that myelocytes frequently occur during diphtheria in children, stating that large numbers (3.6–14.4 per cent. of the white elements) are seen only in severe cases, and indicate a bad prognosis. Türk recently undertook a careful study of their occurrence in infectious diseases, and made accurate daily differential counts of the white blood-corpuscles in a large number of cases. His findings in pneumonia are especially characteristic, namely, a very scanty number of myelocytes or none at all at the beginning of the disease, while at the time of the crisis and immediately after it there are large numbers of them. In isolated cases the increase at this time was very great, and once they amounted to almost 12 per cent. of all neutrophile cells.

2. **Mononuclear eosinophile cells** ("eosinophile myelocytes"), to which H. F. Müller first called attention. These constitute the eosinophile analogues of the preceding group. They are much larger than the polynuclear eosinophiles, though medium-sized, and small examples are frequently found in leukemia. They occur almost regularly in myelogenic leukemia and in anæmia pseudoleukæmica infantum. Apart from these two diseases they are but rarely seen. Mendel found isolated examples, for instance, in a case of myxedema; Türk, in several cases of infectious diseases.

3. **Small Neutrophile Pseudolymphocytes.**—These are about the size of the small lymphocytes, show a round intensely stained nucleus,

and a small amount of protoplasm studded with neutrophile granulations. The deeper staining of the nucleus, the small amount of protoplasm, and the small size of the cell itself, prevent confusion with small myelocytes. These cells, first described by Ehrlich in a case of hemorrhagic small-pox, are extremely rare, and originate by breaking up of the polynuclear cells. The nucleus first divides into three or four parts, and then the whole cell into the same number of fragments. Later, the nucleus of these cells becomes free and the shrunken masses of protoplasm are taken up, especially by the spleen. The free nucleus is likewise apparently destroyed. These cells have also been found in fresh pleuritic exudates, though so far they have been described by no one else, and deserve greater attention since they may be of decided importance in the transitory hyperleukocytoses which have been attributed by some to a breaking up of white blood-corpuscles, by others to a change in their localization.

4. **Irritation Forms** ("Reizungsformen").—These were first described by Türk, and are mononuclear non-granulated cells. They show varying amounts of protoplasm which invariably stains a very intense dark brown with the triacid stain, and a round, simple, frequently excentrically situated nucleus which stains a moderately intense bluish green, and possesses no evident stroma of chromatin. The smallest forms stand between the lymphocytes and the large mononuclear leukocytes, but nearer the former, both in size and general appearance. According to Türk, these cells are frequently found under the same conditions as, and in association with, myelocytes. Their significance can not at present be determined. They possibly represent an early stage of development of the nucleated red blood-corpuscles, as indicated by the intensely stained and homogeneous protoplasm.

This description of white blood-corpuscles by no means exhausts all the forms that occur. It omits entirely the variations in size especially evident among the polynuclear and eosinophile cells represented by dwarf and giant forms. For even with considerable differences in size these cells are always sufficiently characteristic to correspond to the definition of single examples. Moreover, one finds, especially in leukemic blood, isolated cells of very large size which can not be classified, and the significance of which can not be explained.

ORIGIN OF THE WHITE BLOOD-CORPUSCLE.

For the comprehension of the histology of the blood it is of great importance to determine to what degree the three organs, lymph-glands, bone-marrow, and spleen participate in its formation.

The experimental decision of the question by removal of these organs is unfortunately possible only in the case of the spleen. We can, therefore, study the significance of the lymph-glands and the bone-marrow, the removal of which *in toto* is impossible, merely through anatomic and clinical investigations. Moreover, a knowledge of this and similarly complicated questions can only be obtained by a careful combination of animal experiments, anatomic investigations and clinical observations based on considerable material. We can not insist too much on the fact that everyone occupying himself with hematology must first collect the results of a large series of investigations; otherwise the gate of error will surely be left open. The attempt has frequently been made to replace the lack of personal experience by careful theoretic study, but, especially in hematology, this is a fruitless method. Characteristic of this kind of work is the drawing of the widest conclusions from the investigation of a single case. (Example: Troje failed to recognize the lymphocytic character of a case of leukemia which he investigated, and diagnosed it myelogenic leukemia, with the consequence that he denied everything so far determined in relation to this disease, and affirmed the reverse.) It is quite as difficult, as Uskoff's work shows, to avoid error when the conclusions are drawn from animal experimentation without the confirmation of clinical experience. Neither the anatomist nor the physiologist, but the clinician alone is in a position to draw conclusions on this question.

At the introduction to this chapter it was pointed out that a retrograde movement in hematology is in progress which attempts to establish the derivation of all the white blood-cells from the lymphocytes. Omitting embryologic investigations (Saxer), many anatomists as well as physiologists and clinicians have adopted this standpoint. Among the anatomic investigations may be mentioned Gulland's, according to which all varieties of leukocytes are only different stages of development of one and the same element. He differentiates hyaline, acidophile, and basophile cells, and traces all back to the lymphocytes. Arnold supports a similar view, even though in negative form, when he states that a differentiation of the so-called lymphocytes and the polynuclear leukocytes as to their origin on the basis of their form and the appearance of their nuclei is impossible. Moreover, he contends that a classification on the basis of the granulations is not permissible, since the same granules occur in different cells and different granules in the same cell. Gulland's and Arnold's investigations were devoted especially to the differential staining of the granules, and the writer intends to show in

the special discussion of granular cells and the granulations, why he does not refer at greater length to their conclusions.

Experimental researches on this subject have been recently (since 1889) carried out by Uskoff. These led him to see in the white blood-corpuscles different stages of development of one cell, and he differentiated three ages: 1. "Young cells," corresponding to our lymphocytes; 2. "Mature cells" (globules mûrs), large cells with large and irregularly shaped nuclei, which correspond to our large mononuclear and transitional forms; 3. "Old cells" (globules vieux), corresponding to our polynuclear cells. The eosinophile cells are outside the boundaries of this classification.

Among the clinicians, A. Fränkel took up the same trail, and concluded, with Uskoff, on the ground of studies in acute leukemia, which will be described later, that the lymphocytes are young cells, early stages in fact of the other leukocytes. Only a few authorities (like C. S. Engel and Ribbert) have objected to this union of all the forms, and have stood by Ehrlich's old classification. Since, however, a close relationship is insisted upon in numerous works on medicine, the writer will detail in brief the grounds for the separation of the lymphocytes from the bone-marrow group and show the importance of this apparently purely theoretic question to the clinician. The conclusions will be more intelligible and significant if first the part played by the different organs of the hematopoietic system in the formation of the blood, especially of the colorless corpuscles, is carefully considered.

The Spleen.—The question whether the spleen produces white blood-corpuscles has been actively discussed since the first days of hematology.

The endeavor to determine the participation of the spleen in the formation of white blood-corpuscles was first made by counting them in the afferent and efferent vessels, and it was claimed that an increase found in the veins in comparison with the arteries would show the blood-forming power of this organ. Still the results of these counts are very different. The investigators who found an increase in the veins are opposed by others who are equally competent, and to-day no value is attributed to this rough method of investigation.

From later investigations it was demonstrated as a positive fact that after extirpation of the spleen an enlargement of different lymph-glands took place, though the changes in the thyroid gland observed by many cannot be described as constant.

We must mention also blood examinations in animals and man by Mosler, Robin, Winogradow, Zesas, and others after extirpation of the

spleen, which showed that after some time a leukocytosis took place. Investigations were undertaken in the year 1888 by Prof. Kurloff in Ehrlich's Laboratory, in which the behavior of the blood after extirpation of the spleen, was carefully studied. Since this work of Prof. Kurloff has so far appeared only in Russian, its more important results will be detailed. In these investigations Kurloff employed guinea-pigs because they are especially suitable on account of the constant composition of their blood.

In order to understand the investigations and their results, it is necessary first to sketch the normal histology of the blood of the guinea-pig as given by Kurloff.

In the blood of the healthy guinea-pig the following elements are found:

Granular Cells.—*Polynuclear Cells with Pseudo-eosinophile Granulations.*—These granulations, previously found by Ehrlich in rabbits, are readily differentiated from the true eosinophiles by their finer appearance and their different staining with eosin-aurantia-nigrosin. A more important difference, according to Kurloff, consists in the ready solubility of the granules in acid solutions, while they remain unaffected by alkalies. This would indicate that the granulations consist of a basic substance capable of forming soluble salts with acids, The true eosinophile granulations remain unchanged under these tests.

These pseudo-eosinophile polynuclear cells correspond in their function to the polynuclear neutrophiles of man. Their number amounts to 40 to 50 per cent. of all white cells. The place of origin of these cells is apparently the red bone-marrow, since they are found there in large numbers and in all stages of transition from mononuclear granular cells to well-developed polynuclear.

2. *Typical eosinophile leukocytes* corresponding to those of man and amounting to about 1 per cent. of the whites.

3. Cells described by Kurloff as *nigrosinophile cells.* These correspond in their general appearance—that is, the size of the cell and of the granulations—to the eosinophile cells, but are differentiated by a chemic difference, in that the granules take the nigrosin dye when stained by eosin-aurantia-nigrosin, while the eosinophile granules take the red stain. In preparations stained by the triacid mixture the two granulations are also different, in that the nigrosinophiles are stained more blackish.

Nongranular Cells.—*Cells with Vacuoles.*—These cells are especially characteristic of guinea-pig's blood, and show a transformation from large mononuclear to transitional and polynuclear forms while remaining characterized by the lack of granulation. Instead of granules, one finds in the protoplasm of these cells a more or less round nuclear-like figure which takes the nuclear stain, and is possibly an accessory nucleus, though the writer's impression is that it is a vacuole filled with secretory matter of the cell. The development and fate of this speck may be followed through a series of preparations. It appears first as an isolated punctate granule without connection with the nucleus. It gradually enlarges, and when about the size of the nucleus of the cell it (or at least its contents) appears to break through the protoplasm and is discharged from the cell.

The number of these vacuolated cells is 15 to 20 per cent. of the colorless corpuscles.

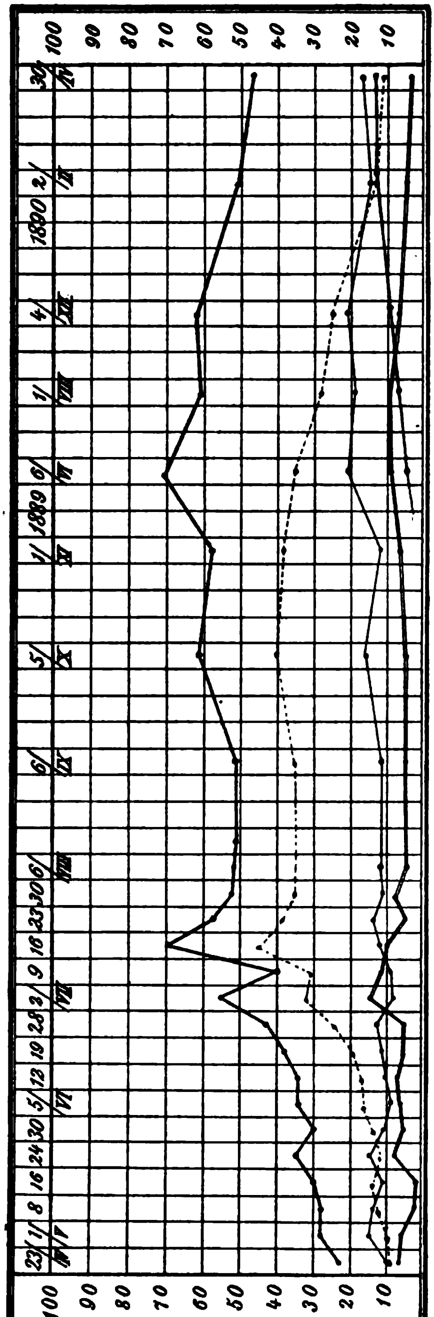

FIG. 4.—Curve of Experiment I. (Compare Table I., p. 60. The curve indicates the relative numbers in the comparative fields.)

The heavy line indicates the number of leukocytes in general.
The light line, the number of nucleated so-called pseudo-eosinophile cells.
The blue line, the lymphocytes.
The double line, the large mononuclear cells.
The red line, the eosinophile cells.

Typical Lymphocytes.—These correspond exactly to the lymphocytes described in man, and amount to 30 to 35 per cent. of all the leukocytes.

Kurloff, in an extremely careful and painstaking investigation, determined the absolute number of leukocytes as well as of the pseudo-eosinophiles, neutrophiles, eosinophiles, vacuolated cells, and lymphocytes, and showed that in uncomplicated cases of extirpation of the spleen in which all inflammatory processes which might increase the polynuclear neutrophile corpuscles were avoided, a gradually progressive increase of the lymphocytes to double and triple their number took place in the course of time, while the number of all the other elements remained unchanged.

Kurloff began his investigation by determining first in a large number of cells (500 to 1000) the relation of the different white blood-corpuscles to one another. But he found it impossible to conclude from one such estimation whether one or another cell-form was increased or diminished. A diminution in the percentage of the lymph-cells, for instance, may be brought about by two factors: 1. By a diminished production of lymphocytes. 2. By an increase in the number of polynuclear cells which naturally diminishes the relative

number of the lymphocytes. It became necessary, therefore, to seek a method which would show the changes in the absolute number of the different forms of leukocytes. Kurloff employed for this purpose a "comparative field" (Vergleichsfeld)—*i. e.*, with the aid of a movable stage he counted the individual forms occurring in a definite area of the preparation (0.22 mm.). This method gives very accurate results provided perfect specimens uniformly spread are employed. The following figures (from Experiment II.) will show the method and its results:

April 12th, counted 52 per cent. of pseudo-eosinophiles; 10 per cent. of lymphocytes.

September 2d (one month after the operation), 22 per cent. of pseudo-eosinophiles.; 58 per cent. of lymphocytes.

By the aid of the comparative field these figures were completed by finding the following averages:

April 12th, 38 white blood-corpuscles—among them, 19.8 were pseudo-eosinophiles, 10.6 were lymphocytes.

September 2d, 81 white blood-corpuscles—among them, 18 were pseudo-eosinophiles, 46.9 were lymphocytes.

From this example it is evident that the total number of white blood-corpuscles was almost double, and that this increase was due entirely to the lymphocytes, while the pseudo-eosinophile cells participated not in the slightest.

The results obtained by Kurloff in this way after extirpation of the spleen may be learned from the report of one of his original experiments, with the curve and the table accompanying it.

Experiment I.—Young female animal, weight 234 grams. Number of red blood-corpuscles in a c.mm. of blood before the operation, 5,780,000; number of white corpuscles, 10,700. On April 19, 1888, the spleen was extirpated, the wound healing by primary intention. The results of the further examinations of the blood are found in the accompanying table:

From the table and curve it appears that the number of white blood-corpuscles more than doubles in the first seven months, owing entirely to an excess of lymphocytes, while the granular or bone-marrow elements and the large mononuclear cells remain constant. The percentage proportions behave somewhat differently. These show an increase in the lymphocytes only from 35 to 66 per cent., while in the case of the other varieties there is an evident fall, for the granular from 44 to 22 per cent., and for the large mononuclear from 18 to 9 per cent. In the course of the second year, for the first time, a considerable relative and absolute increase of the eosinophile cells occurred, the number gradually rising from about 1 per cent. to 28.9 per cent., or in the comparative field from 0.5 to 13.9 per cent. The last blood examination was made on this animal on April 30, 1890—*i. e.*, two years after the removal of the spleen. The animal was entirely healthy, and had delivered

four young ones the product of a splenectomized father. The young showed completely normal spleens and no abnormalities of the blood.

Date.	Leukocytes.		Pseudo-eosinophile cells.		Lymphocytes.		Large mononuclear cells.		Eosinophile cells.		Nigrosinophile cells.	
	Counted.	In the comparative field.	Per cent.	In the comparative field.	Per cent.	In the comparative field.	Per cent.	In the comparative field.	Per cent.	In the comparative field.	Per cent.	In the comparative field.
1888												
April 19	500	. .	44.7	. .	35.4	. .	18.4	. .	1.1	. .	0.5	
" 23	990	24	40.4	9.7	35.6	8.5	21.6	5.2	1.9	0.4	0.4	0.09
May 1 .	858	28	47.0	13.6	32.6	9.1	18.0	5.0	0.9	0.2	0.3	0.08
" 8 .	934	28	45.2	12.6	40.3	11.3	14.3	4.0	0.6	0.2	0.4	0.1
" 16 .	1122	30	38.4	11.5	47.7	14.3	10.3	3.1	3.3	0.9	0.2	0.06
" 24 .	1722	35	40.1	14.0	35.0	12.2	23.6	8.3	1.0	0.3	0.1	0.03
" 30 .	900	30	36.6	10.9	44.4	13.3	18.4	5.5	0.1	0.03	0.3	0.09
June 5 .	825	33	28.4	9.4	49.3	16.2	20.0	6.6	1.7	0.6	0.4	0.1
" 12 .	1314	33	28.0	9.3	49.0	16.2	20.0	6.6	2.2	0.7	0.8	0.3
" 19 .	917	37	32.4	11.9	52.3	19.3	14.5	5.4	0.6	0.3	0.2	0.07
" 28 .	802	42	30.5	12.8	56.4	23.7	11.7	4.9	0.7	0.3	0.4	0.2
July 2 .	1062	56	16.5	9.2	57.1	31.9	25.6	10.3	1.2	0.7	1.2	0.7
" 9 .	1245	51	17.6	8.9	59.1	30.1	21.8	11.1	0.8	0.4	0.8	0.4
" 16 .	974	69	17.5	12.0	66.4	45.8	15.7	10.8	0.2	0.1	0.2	0.1
" 23 .	1156	58	21.7	12.2	67.2	38.9	9.5	5.5	1.5	0.9	0.2	0.1
" 30 .	802	54	20.2	10.7	65.4	34.6	12.8	6.8	1.4	0.7		
Aug. 6 .	910	52	21.7	11.3	67.3	34.9	9.7	4.9	1.0	0.5	0.3	0.2
Sept. 6 .	815	51	23.0	11.7	65.8	33.5	9.8	4.9	0.9	0.5	0.4	0.2
Oct. 5 . .	625	62	26.4	16.3	64.4	39.9	8.5	5.2	0.6	0.4		
Nov. 4 .	800	58	22.5	13.0	66.4	38.5	9.6	7.3	0.9	0.5	0.5	0.2
1889												
April 10	700	. .	29.8	. .	53.3	. .	14.8	. .	1.2	. .	0.6	
June 6 .	900	71	28.2	20.0	50.1	35.6	12.9	9.1	8.2	5.8	0.6	0.4
Aug. 1 .	670	62	30.6	18.9	44.2	27.4	15.2	9.4	9.6	5.9	0.4	0.2
Dec. 4 .	731	63	36.0	22.0	38.3	24.1	11.3	7.1	13.8	8.7	0.6	0.4
1890												
Feb. 2 . .	622	51	32.3	16.5	30.1	15.3	11.1	5.6	26.0	13.2	0.5	0.2
April 30	500	48	36.5	17.5	24.5	11.7	9.4	4.5	28.9	13.9	0.6	0.3

The results of further experiments prove that Experiment I. is not merely an instance of an abnormal occurrence in an isolated animal. These results are given in the following table:

No. of the Experiment.	Number of white blood-corpuscles.		
	Before extirpation of the spleen.	At the close of the first year.	At the close of the second year.
1	10,700	14,200	18,000
2	12,000	27,600	32,000
4	15,000	19,200	19,000
Average. . .	12,600	20,333	23,300

Kurloff obtained the following results from the estimation of the different kinds of white blood-corpuscles:

No. of the experiment.	Before the operation.				At the close of the first year.				At the close of the second year.			
	Polynuclear granular cells.	Lymphocytes.	Mononuclear.	Eosinophiles.	Polynuclear granular cells.	Lymphocytes.	Mononuclear.	Eosinophiles.	Polynuclear granular cells.	Lymphocytes.	Mononuclear.	Eosinophiles.
1	4782	3788	1969	117	4232	7568	2101	170	6570	4410	1692	5202
2	6276	3360	2244	27	5464	16,615	2980	2539	5824	20,861	2688	2240
4	6715	5250	2595	450	6568	10,041	3686	96	7108	3009	2138	7543

From these investigations the writer concludes as follows :

1. In the guinea-pig the spleen is not indispensable to life, since the animals which survive a splenectomy progress normally, and even increase in weight.

2. The hypertrophy and hyperplasia of the lymph-glands, especially of the mesentery, which develop after the operation, are associated with a lymphocytosis that occurs so constantly in the course of the first year after the operation as to constitute a characteristic of the absence of the spleen. This increase in lymphocytes may amount to double the normal or even more. It must be concluded therefore that the removal of the function of the spleen is compensated for by the lymph-glands. This condition of lymphemia may persist exceptionally for years, though in the majority of cases it retrogrades during the course of the first year even to a condition in which a less number of lymphocytes than normal is produced.

3. In contrast to this, the bone-marrow cells, the polynuclear pseudo-eosinophile cells, show not the slightest variation in the course of the first year. Remembering that these occur normally only in the bone-marrow, and that an inflammation in a splenectomized animal shows exactly the same acute pseudo-eosinophile hyperleukocytosis as in a normal animal, it must be confessed that the origin and function of these cells are entirely independent of the spleen and are associated with the bone-marrow.

4. It is especially important to note that the group of so-called mononuclear and allied leukocytes show no evident increase. Since these cells normally occur both in the spleen and in the bone-marrow, it must be assumed that the latter is normally the chief seat of origin, and that the removal of the spleen is therefore easily concealed by a slight increase of marrow activity. According to general biologic experience, if the splenic production were considerable, one would see an overproduction of these cells in the compensating organs.

5. Most interesting is the increase of eosinophile cells which we find constantly in the second year after the operation, and which may be relatively and absolutely very great. Their percentage increased once to 34.6, and their absolute numbers at the end of the second year amounted on an average to 30 to 50 times the original number (see Table).

From Kurloff's investigation, therefore, it is apparent that the spleen plays a very insignificant rôle in the formation of white blood-corpuscles in the guinea-pig, and that after splenectomy compensation is seen during the first year only in the lymph-glands, though in the second year there is also a marked increase in the eosinophile cells. It must be recalled that the spleen has nothing to do with the formation of pseudo-eosinophile polynuclear cells, the analogues of the polynuclear neutrophile cells of man.

The question naturally arises, How do Kurloff's observations, which might be regarded as due to peculiarities of the animal experimented on, compare with those of man?

There is wholly analogous material in cases where splenectomy was done on healthy people as the result of a trauma. Unfortunately this material is rare, and it would be of the greatest value to study the changes in such cases throughout years. The writer himself began such examinations in two patients immediately after the operation, but was prevented from continuing them by death within the first week. According to the statistics of v. Beck, there have been only seven cases of splenic rupture with subsequent splenectomy reported. Of these seven cases, only two, one Riegner's (Breslau), the other v. Beck's (Karlsruhe), recovered. Through the kindness of these gentlemen the writer had the privilege of examining preparations from these two patients.

v. Beck's case was operated on June 15, 1897. A blood preparation was obtained about six months later. The examination showed a marked lymphemia, though for various reasons an exact count could not be made. The preponderating majority of lymphocytes belonged to the large forms. The eosinophiles were assuredly not increased. The writer hopes to have the pleasure of following this case further.

In the case operated on after a trauma on May 17, 1892, and later described by Dr. Riegner, the author has made counts on old and recent preparations. It must be noted that this was not an uncomplicated case, since an amputation of the leg at the thigh was done shortly after the splenectomy on account of gangrene. The following figures were found:

Specimen from	Polynuclear.	Lymphocytes.	Eosinophiles.	Large mononuclear.
June 12, 1892 . .	81.9 per cent.	15.9 per cent.	1.3 per cent.	
Oct. 11, 1892 . . .	8 "	13.7 "	4 "	1.7 per cent.
Sept., 1897	56.8 "	33.1 "	3.5 "	1.5 "

It is to be regretted that preparations at hand are only from the beginning and the end of the five years' period of observation. From Riegner's own communication it appears that the lymphocytosis in this case set in one month after the operation and persisted for a long time, as in certain cases of Kurloff's in animals. The increase in the lymphocytes at the end of the five years is particularly remarkable. The eosinophile cells fluctuated at this period at the upper boundary of normal. According to all experience, it is probable that they underwent an intercurrent elevation in number in the meantime.

Cases in which a splenectomy was done on account of disease of the spleen are more frequent. Among these the cases of splenic cysts would theoretically give the most significant results because the part of the spleen not affected by the cystic formation frequently shows normal structure, and accordingly possesses functional power. The removal of chronic splenic tumors, on the contrary, is of no value as far as the blood-finding is concerned, since the function of the spleen may have been lost long before on account of the pathologic changes.

Among instances of the latter kind may be mentioned the well-known and carefully observed cases of B. Credé, in which the organ was extirpated in a forty-four year old man on account of large splenic cysts. Within two months after the operation there developed a leukemic condition of the blood brought about exclusively by an increase of lymphocytes, as is shown by Credé's communication and the accompanying Table. Four weeks after the operation a painful doughy swelling of the thyroid gland occurred, which, with fluctuations in intensity, persisted almost four months. This retrogressed almost to normal simultaneously with the general recuperation of the patient. This swelling of the thyroid gland, though it undoubtedly stands in the closest relation to the splenectomy, and is of the greatest interest, is not a regular accompaniment of this operation, as it failed to occur, for instance, in v. Beck's case. [Warthin's interesting observations on hemolymph glands will be referred to in the section on Pernicious Anemia.—Ed.]

The latest communications on extirpation for disease of the spleen come from Hartmann and Vaquez. From their investigations one learns the following: 1. A slight post-operative increase of the red blood-corpuscles and a genuine though very transitory acute hyperleukocytosis. 2. A primary decrease in hemoglobin, which gradually rises again to normal. 3. After four to eight weeks a lymphocytosis of varying duration. 4. A moderate eosinophilia occurring late,—after many months.

The author has had the opportunity of examining three such cases:

The first was a patient (Mrs. St.) who was examined in company with Oberarzt Dr. A. Neumann, and whose spleen was removed by E. Hahn on Feb. 8, 1895, on account of an echinococcus cyst. It is to be assumed that even before the operation the spleen did not functionate normally. On Sept. 2, 1897, the following percentages were found:

Polynuclear neutrophiles	76.8 per cent.
Lymphocytes	18.4 "
Eosinophiles	3.4 "
Large mononuclears	1.1 "
Mast-cells	0.4 "

These were almost normal conditions. Still, it must be added that the patient manifested a beginning phthisis pulmonum, to which a relative increase of the polynuclear elements must be attributed, and without which the percentage of lymphocytes and eosinophiles would probably have been higher.

For the knowledge of two other cases thanks are due Prof. Jonnescu, of Bucharest. One case was that of a man about forty years of age, in whom the spleen was extirpated on Sept. 27, 1897, on account of splenomegaly. Healing was by primary intention. The white blood-corpuscles were persistently increased. The proportion of the whites to the reds was 1 : 120 to 1 : 130; the number of reds averaged 3,000,000. Examination of specimens obtained two months after the operation showed a decided lymphemia, large lymphocytes preponderating. The eosinophiles and mast-cells were evidently increased. More exact estimations of numbers are not permissible because the specimen was not uniformly spread.

From the second case, which was likewise operated on on account of splenomegaly, only very much injured specimens were obtained. Still, it could be determined with certainty that there was no considerable increase of lymphocytes, while the number of eosinophiles was evidently, the number of mast-cells to a less degree, augmented. It is probable that the increase of these last two was not the result of the splenectomy, but rather the expression of reactive changes brought about by the disappearance of the splenic function before the operation.

[In a personal observation of a case of splenomegaly I found large numbers of eosinophile cells before operation, at a time when the disease was doubtless of over a year's duration. After the operation there was at first a reduction of the percentage as well as actual numbers, and for a time a polymorphonuclear leukocytosis (pneumonic). Subsequently the eosinophilia reappeared and was present three months after the operation.—ED.]

These cases of splenectomy furnish a criterion for chronic diseases of the spleen. For although it is very difficult in these cases to make positive statements, since it is never known to what extent the individual organs have been injured or influenced by the general disease, an increase of the lymphocytes (provided disease of the lymphatic glands is excluded) would point to functional abrogation of the spleen.

If, on the contrary, in a case of chronic splenic tumor an increase in the eosinophile cells is found, this would be attributable to Kurloff's secondary reaction of the bone-marrow. Several such cases may be found in the literature; for instance, Müller and Rieder mention three

cases of tumor lienis caused by congenital lues, hepatic cirrhosis, and a neoplasm of the skull cavity, respectively, in which the eosinophiles amounted to 12.3 per cent., 7 per cent., and 6.5 per cent.; while in three cases of acute splenic tumor associated with typhoid fever the percentages varied from 0.31 to a maximum of 0.82. These writers ask the question, since Ehrlich insists that the probable source of the eosinophile cells is the bone-marrow, "Does this increase of the eosinophile cells stand in relation to the splenic tumor or to a participation of the bone-marrow, the function of which has been increased in order to compensate for the greater or less loss of blood-formation produced by the (functionally) extirpated spleen?"

From what has been shown there can be no doubt that the question has been decided according to Ehrlich's view.

What then are the physiologic functions of the spleen since they are unnecessary to the preservation of life? Its chief rôle seems to be to take up the fragments of the red and white blood-corpuscles broken up in the circulation so that the organism will not entirely lose this valuable material. Ponfick, for instance, has demonstrated that on destruction of the red blood-corpuscles the spleen takes up a part of the "shadows," and he therefore designated the enlargement as a spodogenous splenic tumor (*σπόδος*, ashes, débris). Ehrlich brought forward a corresponding demonstration in regard to the products of destruction of the white blood-corpuscles, and showed that the splenic tumor seen in infectious diseases and in phosphorus-poisoning is to a great extent produced by the parenchyma of the spleen taking up the débris of the neutrophile cells.

The relation of the spleen to a new formation of red blood-corpuscles is one of the problems of comparative anatomy. Results found in one animal can not be applied to others. In the lower vertebrates, as fishes, frogs, turtles, and even birds, the blood-making power of the spleen is of great importance, while in mammalia it has little if any significance. One finds nucleated red blood-corpuscles in the spleens of normal mice in relatively large numbers; they are scanty and often found only on careful examination in those of rabbits. In the spleens of dogs they are physiologically absent, but may be found after an anemia has been produced by hemorrhage; while in the human spleen they are found neither normally nor in cases of severe anemia, but only in leukemia. U. Gabbi, in his very recent communication on the hemolytic function of the spleen, emphasizes the difference between the different species of animals. In guinea-pigs he found that the spleen exercised a pronounced destructive action upon the red blood-corpuscles, while in

rabbits this faculty was only suggested. Corresponding to this, in splenectomized guinea-pigs the number of red blood-corpuscles increased on an average 377,000 per c.mm., the amount of hemoglobin 8.2 per cent.; in splenectomized rabbits this increase was wanting.

Considering all of the foregoing results, it must be concluded that the function of the spleen in the production of white blood-corpuscles can not be great, and that if white cells are produced by it these must be free from granules. Consequently the spleen stands in a closer relation to the lymphatic system than to the bone-marrow. There is assuredly not the slightest relation of the spleen to ordinary leukocytosis.[1]

The Lymph-glands.—Since it is impossible to remove experimentally all the lymph-glands, one is constrained to study their participation in the formation of blood almost entirely in clinical and anatomic investigations.

The view that the lymphocytes of the blood, both large and small, are identical with those of the lymph-glands and lymphatic apparatus generally, has remained uncontested since Virchow's description of them, and it must be evident to everyone from the complete correspondence of their morphology, the staining properties manifested by the protoplasm and nucleus, and the absence of granulations.

The view that the lymphocytes of the blood actually originate in the lymphatic system is supported by numerous clinical observations. Ehrlich some time ago drew attention to the fact that when extensive portions of the lymph-gland system were damaged by disease the number of lymphocytes may be considerably diminished, and this has been frequently confirmed by different writers. Reinbach described several cases of malignant tumors, especially sarcoma, in which the percentage of lymphocytes (normally about 25) was decidedly diminished—*e. g.*, a case of lymphosarcoma colli, in which they amounted to only 0.6 per cent. This finding may be readily explained by the disappearance of function of the lymph-glands. How the advocates of the theory that the lymphocytes are early stages of the other white blood-corpuscles deal with this fact is difficult to under-

[1] C. S. Engel has recently proposed to designate acute leukocytosis as "lienal leukocytosis," analogously to the clinical conception of lienal leukemia. This name would be appropriate only if the polynuclear cells originated in the spleen, an assumption which even Engel does not consider, since he expressly insists that no conclusion in regard to the origin of these cells should be drawn from the designation. Since, however, as will be shown in the next section, acute leukocytosis is referable exclusively to the bone-marrow, the designation lienal leukocytosis seems absolutely wrong because it would lead to an entirely erroneous conception as to the origin of leukocytes.

stand. The only thing they can say is, that the lymphocytes in such cases are rapidly transformed into the older forms of polynuclear elements, or, in Uskoff's words, there is a precipitate maturity of the lymphocytes.

[Wolff[1] believes that there are formed in all the blood-making organs cells similar to lymphocytes, but capable of developing into different forms of leukocytes. As a rule, the different blood-making organs have individual function, but in case of necessity they are capable of vicarious action, and thus in certain anemias, like that of lead-poisoning, the spleen may have myeloid action. He claims to have discovered in cases of leukemia under his observation transitional conditions between lymphoid and myeloid disease. Further reference to the origin of lymphoid cells will be made in reference to leukemia.—ED.]

Further proofs of the origin of the lymphocytes from the lymph-glands are found in cases which show an increase in lymphocytes. These "lymphocytoses" are rare in comparison with other leukocytoses. They are found most commonly in conditions associated with a hyperplasia of the lymphatic apparatus. Ehrlich and Karewski, in a work not yet published, examined a large number of typical cases of lymphoma malignum, and found regularly a lymphocytosis which was sometimes so marked as almost to simulate leukemia.

Supported by this fact, Ehrlich and Wassermann,[2] in the case of a rare skin disease, made the diagnosis, *in vivo*, of a malignant lymphoma merely from the absolute increase of the lymphocytes, although no swelling of the glands was palpable. The principal post-mortem finding was a tumor of the retroperitoneal lymph-glands the size of one's fist.

Moreover, the lymphocytosis occurring after extirpation of the spleen (see above) belongs here, since it is invariably associated with vicarious enlargement of the lymph-glands.

In the investigation of the conditions under which a greater number of lymphocytes appear in the circulation during health, one's attention is attracted naturally to the digestive tract, the wall of which contains large amounts of lymphatic tissue. In digestive leukocytosis, according to Rieder, the proportion of lymphocytes to polynuclear cells remains about normal, though it fluctuates rather in favor of the lymphocytes, while there is a marked relative diminution of the eosinophiles. The digestive leukocytoses, therefore, are evidently differentiated from those in which the neutrophile elements alone are increased. The simultaneous increase of lymphocytes and polynuclear

[1] *Zeit. f. klin. Med.*, 1902, vol. xlv., p. 385.
[2] *Dermatolog. Zeitschr.*, 1894, vol. i.

cells is apparently the result of a superaddition of lymphocytes to an ordinary leukocytosis produced by assimilated metabolic products.

The influence of the digestive tract is still more striking in certain diseases, especially the intestinal diseases of nurslings. For instance, Weiss found in simple gastric and intestinal catarrhs a considerable increase of white blood-corpuscles, due principally to lymphocytes.

According to the late observations of Meunier, whooping-cough may be mentioned among the small number of diseases associated with a pronounced lymphemia. In the convulsive stage of this disease both the polynuclear cells and the lymphocytes are increased, the latter to a predominating degree; the increase of the former being about double, of the latter four times the normal. Meunier is probably correct in attributing this lymphocytosis to the irritation and swelling of the tracheobronchial glands.

An increase of lymphocytes from chemic irritation is extremely rare, while there are a number of substances (bacterial products, protein, nuclein, organic extracts, etc.) capable of producing polynuclear leukocytosis. In very isolated cases an increase in lymphocytes has been seen following an injection of tuberculin in tuberculous individuals (E. Grawitz); yet on account of the rarity of these cases it can scarcely be doubted that a latent tuberculosis of the glands participates, and the increased number of lymphocytes is produced not by the chemic properties of the tuberculin, but by an extensive specific reaction on the part of the diseased glands.

Only one single substance has so far been mentioned in the literature as capable of producing lymphocytosis, namely, pilocarpin. Walstein claims that he produced lymphemia by injections of pilocarpin, and that a progressive increase in lymphocytes followed repeated injections.

Lymphocytosis, therefore, stands in sharp contrast to ordinary leukocytoses, for while the latter are incontestably the expression of chemotaxis—*i. e.*, the action of soluble substances on the bone-marrow—lymphocytosis is due to a local irritation of lymph-glands. Consequently one must refer the increase in lymphocytes in digestive leukocytoses, and in the intestinal diseases of children, to the irritation of the lymphatic apparatus of the intestine, and that following the injection of tuberculin to the reaction of diseased lymph-glands. Accordingly one is obliged to conclude that a lymphocytosis occurs when in response to an increased circulation of lymph in a greater or less extensive lymphatic region, more elements are mechanically forced from the lymph-glands. The pilocarpin lymphocytosis furnishes no argument against this view, since pilocarpin produces an extraordinary decrease,

even though transient, in the general amount of water, on account of which fluid containing lymph-cells is readily forced into the blood. We must, therefore, consider lymphocytosis as the result of a mechanical process; leukocytosis, as the expression of a chemotactic reaction on the part of the polynuclear cells.

The best support for this theory is found in the fact that the polynuclear leukocytes possess a lively ameboid motility which is wanting in the lymphocytes. [A number of investigators (Maximow, Almkoist, Hirschfeld, Flexner and Bunting, Welch, Kelly) either observed ameboid movements or were able to bring forward indirect evidence of such movements on the part of the lymphocytes. There seems little doubt of the accuracy of this view.—ED.]

Corresponding to this lack of motility, one finds that the lymphocytes, in contrast to the polynuclear neutrophiles and oxyphiles, are unable, in inflammatory processes, to leave the vessels. An experiment that is very interesting in this connection was described years ago by Neumann. This investigator produced suppuration in a patient with lymphatic leukemia, whose blood contained only a very small number of polynuclear cells. Examination of the pus showed that it consisted exclusively of polynuclear cells, and that not a single one of the numerous lymphocytes present in the blood appeared in the exudate.

Similar results—*i. e.*, polynuclear elements alone—are found on histologic examination of all recent inflammatory processes. That a small-cell infiltration, consisting apparently of lymph-cells, appears in the course of the inflammation, is well known, yet this by no means proves that they wandered out from the vessels. This is not the place for a review of the prolific controversy in regard to these small cells, and the authors must content themselves with a reference to the very recent thorough work of Ribbert. Ribbert regards these collections of small cells as analogues of lymph-nodules, and attributes their formation to an increase in size of the lymphatic foci which were present normally though less developed.

Therefore, we must conclude from clinical and morphologic investigation, as well as from observation of inflammatory processes, that the lymphocytes stand in no reciprocal relation to the polynuclear leukocytes. In the following section we shall arrive at the same conclusion in another way.

The Bone-marrow.—The spleen and lymph-glands alone were considered the breeding-places of blood-corpuscles until the almost simultaneous investigations of Neumann and Bizzozero drew general attention to the bone-marrow by showing that the advance stages of the

red blood-corpuscles were found there. This discovery was quickly recognized and applied to pathology by Cohnheim and others. The demonstration that after severe hemorrhage the yellow marrow of the long tubular bones was transformed again into red marrow, showing an increased demand on the regenerative function of the bone-marrow, was especially valuable in this regard.

The writers know of no other locality in man where red blood-corpuscles are formed, though in other mammalia, as was mentioned previously (p. 81), the spleen plays a slight rôle in their formation. The type which the formation of erythrocytes follows normally in adults and the differences manifested in pernicious anemia have been described in detail in the chapter on the Red Blood-corpuscles. There it was shown that according to Ehrlich's view the formation of erythrocytes in Biermer's anemia follows a type analogous to that in the embryo.

In this section we are concerned especially with the white blood-corpuscles and their connection with the bone-marrow. In man, as well as in a large number of animals (*e. g.*, apes, guinea-pigs, rabbits, doves, etc.), the cells produced by the bone-marrow invariably show specific granulations in sharp contrast to those produced by the lymphatic system, which in all animals are non-granulated.

The granular cells of the bone-marrow are conveniently divisible into two groups:

The first group, constituted by the so-called *specific granular* cells, is of most importance on account of the fact that because of morphologic and tinctorial differences it is characteristic of certain species of animals. For instance, in man and in apes the cells show neutrophile granulations; in guinea-pigs and rabbits there are the pseudo-eosinophiles described by Kurloff; in birds two specific granulations, both oxyphilic, one in crystal form, the other in granules. The varieties of specific granules investigated so far have this in common, that they are stained by acid or neutral stains, and show scarcely any affinity for basic dyes. The great importance of these cells is evident from the fact that they far exceed in number the other bone-marrow elements in all species of animals.

The second group of bone-marrow cells contains granules common to the whole series of vertebrates, from the frog to man, and is, therefore, not characteristic in any individual species. This is made up of: 1. Eosinophiles; 2. Basophile mast-cells.

The non-granulated cells of the bone-marrow are represented generally by mononuclear forms of different types. Their number and sig-

nificance are less marked than in the case of the granulated cells of the first group.

Among these non-granular cells, *giant-cells* require special mention, since they are an almost constant constitutent of the bone-marrow in mammalia. According to the recent investigations of Pugliese, in the hedge-hog, the giant-cells of the bone-marrow increase considerably after extirpation of the spleen. In this animal the spleen is of extraordinary size, and accordingly seems to fulfil a much more important hematopoietic function. Pugliese claims that in splenectomized hedgehogs the nucleated giant-cells are transformed into leukocytes by amitotic nuclear division. Unfortunately in this preliminary communication there is no notice taken of the granules in the bone-marrow cells.

When a stained preparation of bone-marrow, for instance, from guinea-pigs, rabbits, or man, is examined, the characteristic finely granulated cells are found in all stages of development from the mononuclear through the transition-forms to the polynuclear (polymorphonuclear), just the same as in the circulating blood. Moreover, one glance is sufficient to show that the bone-marrow is evidently the breeding-place where typical polynuclear cells are formed from granular mononuclear cells.

The polynuclear eosinophile leukocytes may be seen undergoing a similar maturation.

By special staining Ehrlich was able to show that during the transformation of mononuclear cells to polynuclear the properties of the granules changed. When young, the cells show a predominance of basophile granules which gradually disappear on the maturing of the cells. For instance, the pseudo-eosinophile granules of the mononuclear cells of the rabbit, stained after long fixation at a high temperature in a steam sterilizer, appeared, with eosin-methylene-blue, bluish red. In the transitional stages they gradually lost this mixed color, and in the polynuclear leukocytes stained pure red. Analogous observations have been made on the eosinophile cells of man and animals, and on the neutrophile cells of man. It is, therefore, possible to decide from an isolated granule whether it belonged to a young or an old cell.

How rapidly the mononuclear cells go over into the polynuclear, and whether the maturation of the granules invariably corresponds to that of the whole cell, can not be stated with certainty. Still, on the ground of the writers' observations, it may be assumed that ordinarily both mature simultaneously, though in special cases the maturation of the cell may be more rapid than that of the granules. These observations

can readily be made on eosinophile cells. It was, for instance, mentioned by Ehrlich in his first work (1878) that besides the typical eosinophile granules, isolated granules were frequently found which showed a different behavior to the stain; for example, which would stain more black in eosin-aurantia-nigrosin, bluish-red to pure blue in eosin-methylene-blue. Even then Ehrlich described these as young elements. Similar phenomena are seen in both the neutrophiles and eosinophiles of the circulating blood in leukemia. Ehrlich repeatedly found in leukemic blood polynuclear eosinophile cells containing almost exclusively young[1] granules.

Ehrlich attributed this to atypical hastening of maturation on the part of the cell and a comparatively slow development of the granules.

One sees in normal blood only the mature forms of the specific granular leukocytes ordinarily found in the bone-marrow, and never the mononuclear and transition-forms of the neutrophile group.

Since the latter are found exclusively in the bone-marrow, and never in the spleen and lymph-glands, Ehrlich considered them the most characteristic cells of the bone-marrow, and, *κατἐξοχήν*, designated them "myelocytes."[2] Considerable numbers of myelocytes, no matter what the size, are found in the blood of adults practically only in myelogenic leukemia (the rare exceptions to this which could never be confused with leukemia, are stated on pp. 68 and 69).

The same is true of the eosinophile cells in that the mononuclear varieties which may be described as eosinophile myelocytes occur almost

[1] This double staining of the eosinophile granules has been interpreted by many writers, for instance, Arnold, to indicate that eosinophile and mast-cell granulations occurred in the one cell. That this is not the case is evident from the fact that in metachromatic staining the "basophile" granulations of the eosinophile cells do not show the metachromasia characteristic of the mast-cells.

[2] Recently A. Fränkel reported a series of histologic investigations in which he succeeded in one single case in finding genuine myelocytes within inflamed lymph-glands. He says (XV. Congress f. innere Medicin): "A short time ago I had a series of methodical investigations made by my assistant, Dr. Japha, on the granulation of the leukocytes in the lymph-glands in a large number of infectious diseases, like scarlet fever, diphtheria, and typhoid fever, which were associated with acute swelling of the glands. These investigations were made on cover-glass specimens prepared from the juice of the glands removed immediately after death and stained by Erhlich's triacid mixture. In a large number of cases so examined, only one, an instance of scarlet fever, showed mononuclear cells with neutrophile granulations. This case, however, was unquestionable." The extraordinary rarity of this finding convinces the writers that the formation of neutrophile mononuclear elements can not be regarded as a normal function of lymph-glands. Polynuclear neutrophile cells invariably occur in inflamed lymph-glands, but naturally only as elements which have wandered in in response to the inflammation. That polynuclear neutrophile leukocytes may be transformed in the tissue into mononuclear, is demonstrated by every pus preparation, and this may explain Japha's isolated observation.

exclusively in leukemic blood. These forms, first observed by H. F. Müller, are of less diagnostic value, since the principal foreign elements in the blood in myelogenic leukemia are Ehrlich's myelocytes.

Very important conclusions regarding the question of leukocytosis may be deduced from these observations. Recalling that polynuclear neutrophile cells develop and are stored only in the bone-marrow, and that in the ordinary leukocytoses they alone are increased, it becomes clear that leukocytosis is purely a function of the bone-marrow, as Ehrlich has always insisted. Moreover, the sudden occurrence of leukocytosis, as frequently seen in diseased conditions and experiments, can be satisfactorily explained only in this way. It is impossible to believe that in the period of time in which leukocytosis develops, often only a few minutes, new formation of leukocytes could occur; consequently there must be a storage place for those cells ready formed and capable of wandering out on any suitable irritation. This place is the bone-marrow, and the bone-marrow alone. Here all mononuclear cells gradually mature to polynuclear contractile cells which respond to chemotactic irritation by emigration, and so produce acute leukocytosis.

The bone-marrow, therefore, fulfils, besides others, the highly important purpose of a protective organ from which injurious influences attacking the organism can be quickly and energetically combated, just as in a fire-station help is continually at hand to respond to the signal of danger from any locality.

The fact has still to be noted that the large mononuclear leukocytes and the transitional cells of normal blood do not increase in ordinary leukocytoses. In fact, in high grades of leukocytosis their percentages may be actually diminished on account of the increase of the polynuclear cells. It appears, therefore, that these elements do not respond to chemotactic irritation, and probably enter the blood in a different way from that of the polynuclear cells.

The authors believe that the non-granular mononuclear cells of man are analogous to those described by Kurloff in guinea-pigs (see p. 73); though Kurloff's cells in their transformation remain non-granular, while the mononuclear cells of man eventually become neutrophile granulated polynuclear cells. In the acute leukocytosis of guinea-pigs only the pseudo-eosinophile polynuclear cells which emigrate as such from the bone-marrow are increased, not the polynuclear non-granular cells which grow to maturity in the blood. The special characteristics of guinea-pigs' blood, in which two varieties of polynuclear cells remain recognizable, clear up the obscurity of the corresponding conditions in human blood, where interpretation is more difficult on account of the polynuclear neutrophiles showing a double genesis, the majority coming ready-formed from the bone-marrow, a small minority being formed within the circulation from the mononuclear and transitional forms.

Nothing is known with certainty as to the place of formation of the non-granular large mononuclear leukocytes.

It has been demonstrated by Kurloff that these cells occur in guinea-pigs in both the bone-marow and spleen, and that after extirpation of the spleen their absolute number is not changed. The bone-marrow is, therefore, capable in guinea-pigs of preserving the normal balance of the large mononuclear non-granular cells in the blood.

The authors' estimations of these cells in human blood after splenectomy gave normal numbers. One may, therefore, assume that the great majority of large mononuclear non-granular cells of human blood likewise originate in the bone-marrow.

Still, on account of their small number and their not very evident characteristics, they are extremely difficult to point out in the midst of the different varieties of cells in the bone-marrow. Thorough investigation of their origin is, therefore, almost impossible, and will probably be successful only when an experimental disease is found which is capable of producing an important increase of this variety of cell. This is not beyond the range of probability, since an absolute increase of the large mononuclear cells has been observed in man in the post-febrile stage of measles.

From microscopic investigations, therefore, the conclusion may be reached that the bone-marrow is by far the most important organ in the formation of blood, since it alone produces the red blood-corpuscles and the chief group of the white corpuscles, namely, the polynuclear neutrophiles.

Experimental investigation of the bone-marrow function presents unconquerable difficulties. The removal of the entire bone-marrow, or even of a large part of it, is an impossible operation. Moreover, comparative estimations of the corpuscles in the arterial and venous blood of bone-marrow are without value. J. P. Roietzky, under Uskoff's direction, recently made a series of investigations on the blood of the nutritive artery of the tibia and its corresponding vein in dogs. He found that the number of white blood-corpuscles was somewhat larger in the vein, but that the absolute number of "young blood-corpuscles" (Uskoff)—*i. e.*, of lymphocytes—was considerably diminished, while the number of "mature" cells, corresponding in great part to our polynuclear, was considerably increased. He presents the following table:

	Whole number.	Young corpuscles.	Mature corpuscles.	Old corpuscles.
Arterial blood	15,000	1950 (13 per cent.)	840 (5.6 per cent.)	12,210 (81 per cent.)
Venous "	16,400	656 (4 ")	2788 (17 ")	12,956 (79 ")

In making such estimations it is necessary to assume that there is continuous function on the part of the bone-marrow. But if the bone-marrow continuously reduced the number of the lymphocytes to such extent, it would be impossible to understand how with the extent of the bone-marrow and the rapidity of the circulation the normal condition of the blood would be preserved. Consequently everything speaks for the fact that the bone-marrow functionates interruptedly, inasmuch as the elements are continually maturing in the bone-marrow and are thrown off only at certain times in response to chemic irritation. This consideration at once shows how little is to be expected from investigations like that of Roietzky's.[1]

The clinical study of cases in which considerable portions of the bone-marrow are replaced by other kinds of tissue is much more important. These cases are divisible into two groups: 1. Malignant tumors of the bone-marrow. 2. So-called acute leukemia.

Unfortunately but few available observations have so far been made in regard to the first group, and there are still fewer cases in which the entire bone-marrow was subjected to an exhaustive examination, which alone would show the extent of the defect.

The changes produced by tumors are divisible into two groups according to the blood-findings. The first is represented by a case published by Nothnagel in his well-known work on *Lymphadenia ossium.* In this the blood showed during life merely the signs of a simple severe anemia with isolated normoblasts, a moderate leukocytosis, and no myelocytes. The autopsy showed complete disappearance of the bone-marrow and its replacement by tumor masses. In this case, therefore, the blood-finding *in vivo* was completely explained by the abrogation of the bone-marrow function. Nothnagel expresses the opinion that the vicarious formation of the nucleated red blood-corpuscles in the spleen is followed by that of the leukocytes in the lymph-glands.

The second group is exemplified by J. Epstein's case recently reported from Neusser's clinic, and by that of Israel and Leyden. In this group the blood shows, in addition to the ordinary anemic changes, others partially characteristic of myelogenic leukemia. In Epstein's case of metastatic carcinoma of the bone-marrow a marked anemia was found associated with very many nucleated red blood-corpuscles of both normoblastic and megaloblastic type, the nuclei of which showed the strangest

[1] Moreover, the whole foundation is withdrawn from Roietzky's studies by the statement of Geheimrath Prof. Schütz, that the tibiæ of all dogs contain no red marrow, but only yellow marrow, which, as is well known, exercises not the slightest hematopoietic function.

figures, due not only to typical nuclear division, but also to nuclear destruction. The white blood-corpuscles were decidedly increased, showing a relation to the reds of $\frac{1}{25\text{-}40}$. This increase was most evident in the large mononuclear forms, the greater number of which showed neutrophile granulations; in other words, belonged among the myelocytes. Only two eosinophile cells were found in all the preparations.[1]

As Epstein correctly points out, the explanation of such a blood picture, apart from the purely anemic changes, is not easy. The occurrence of myelocytes is most readily explained by direct irritation of the remaining bone-marrow by the surrounding tumor masses. Moreover, in this irritation the mechanical factor is of less importance than the highly concentrated metabolic chemic products of the tumor which act on the motile cells in a negatively chemotactic way. This view is supported by Reinbach's careful investigation of the behavior of leukocytes in malignant tumors. In forty cases myelocytes were found in the blood only once (in a case of lymphosarcoma complicated with tuberculosis), when they amounted to about 0.5 to 1 per cent. of the white blood-corpuscles. The autopsy showed isolated yellowish-white tumor foci up to the size of a dime in the bone-marrow. When one considers that in none of the other thirty-nine cases myelocytes were found, there need be no hesitation in explaining their presence in the blood in this single instance as a result of the bone-marrow metastases. Moreover, the limited distribution of the metastases explains the small number of myelocytes.

In the interpretation of the megaloblasts in this case what has been said in another section on the nature and the significance of these cells must be remembered. They are not found in normal bone-marrow, but, according to the theory of the authors, originate only when specific influences, which must be assumed to be present in pernicious forms of anemia, act on the bone-marrow. Therefore, in cases of tumor anemia in which megaloblasts are found in large numbers in the blood, one must assume that the chemic irritant which incites the formation of megaloblasts in the bone-marrow comes from the tumor.

Yet the presence of megaloblasts in the bone-marrow does not necessitate their occurrence in the blood, as is frequently shown by pernicious anemia, in which the bone-marrow may be packed with megaloblasts, while only isolated specimens are found in the blood. Whether the passage of the megaloblasts from the bone-marrow into the circulation is

[1] We call particular attention to the small number of eosinophile cells, because, according to Ehrlich's postulates, this want of eosinophile cells is incompatible with the diagnosis of leukemia.

attributable generally, as in Epstein's case, to chemic irritation, or is the result of mechanical causes—*e. g.*, a washing out—can not at present be decided.

In addition, the bone-marrow may be replaced by typical lymphatic tissue. In fact, corresponding to the well-known statements of Neumann, which have been generally confirmed, this regularly takes place in lymphatic leukemia. In these cases large portions of the bone-marrow are replaced not by malignant tumor masses, but by a tissue incapable of exercising irritative effects (such as those described above) on the remaining myeloid tissue. To this circumstance must be ascribed the fact that in these very cases of lymphatic degeneration of the bone-marrow the distinguishing symptoms are observed in their purest form.[1]

The most important data are obtained from a study of acute (lymphatic) leukemia, the frequent occurrence of which was first emphasized by Epstein, while the disease itself has recently been thoroughly investigated by A. Fränkel. Acute leukemia is pre-eminently suited to this purpose, for the reason that the abnormal growth of lymphatic tissue occurs very rapidly, and therefore produces a rapid and uncomplicated abrogation of function of the bone-marrow. Under its influence the neutrophile elements of the bone-marrow disappear so rapidly and sometimes so completely, that a single myelocyte may be found only after a long search (as in one case of Ehrlich's). That the blood must show in such a case a marked diminution in the absolute number of the polynuclear leukocytes, is evident from the fact that these cells arise from the bone-marrow, and this being destroyed, no more can appear in the blood.

Dock came to similar conclusions, and explains in a corresponding way the lack of neutrophile cells in lymphatic leukemia, from the replacement of the myeloid tissue by lymphatic tissue.

Lymphatic leukemia consequently furnishes a striking proof that the lymphocytes represent a particular variety of cells with no relation to the polynuclear cell. It is, therefore, decidedly surprising when A. Fränkel, after a critical and careful examination of eight cases of acute lymphatic leukemia, finds in them grounds for the assumption that the lymphocytes go over into polynuclear cells. This can be explained only by the confusion created by Uskoff's teaching in regard to the

[1] As a contrast to this lymphatic metamorphosis of the bone-marrow one finds in myelogenic leukemia a myeloid transformation of the other blood-making organs, particularly the lymph-glands, which is characterized by the presence of myelocytes, eosinophiles, and nucleated red blood-corpuscles.

"young cells." The authors define lymphocytosis as an increase of lymphocytes in the blood; Fränkel regards it in Uskoff's sense as the appearance of the young forms of the white blood-corpuscles in the blood. Following this out, he attributes the decrease of polynuclear cells in this disease to "disturbance of the conditions necessary for the transformation of the young forms." Still if the lymphocytes are considered young forms and the polynuclear cells older stages, the true conditions would be more correctly represented if we spoke in lymphatic leukemia, not of a disturbance, but of an absolute prevention of the process of maturation. Yet easy as it is to picture an irritation or injury which can produce a hastening of the normal process, in other words, a premature maturation, it is very difficult to conceive of conditions which would prevent the natural maturing of the elements. The discovery of such conditions would be epoch-making for both biology and therapy. The only way out of this dilemma would be to assume a premature death of the lymphocytes, but for this there is not the slightest evidence, even in Fränkel's monograph. Fränkel makes the difference between acute and chronic leukemia to be "that in the former the newly formed elements are thrown off from their place of origin into the circulation with such extraordinary rapidity that time is wanting for complete development, while in chronic leukemia the transition is probably much slower." This explanation is plainly contradictory to the facts, since there are chronic forms of lymphatic leukemia which show the microscopic picture of acute leukemia. The foundation is therefore removed from Fränkel's whole deduction. [The view of those who believe in the essential unity of all forms of leukocytes is based partly upon the alleged discovery of transitional cells, and partly upon the occurrence of lymphemic leukemia in cases in which the bone-marrow alone has been found diseased. Further, it is contended that the old belief in the lack of ameboid movement on the part of the lymphocytes is fallacious. With regard to the theories of the origin of the leukocytes, Pappenheim states that the large lymphocyte is the mother cell of all forms of leukocytes, the characteristic parenchymatous cell of all reticular tissues, and therefore of the bone-marrow. The red corpuscles also are derivatives of these mother cells. With regard to the rôle of the bone-marrow in the production of lymphemic conditions, it may be recalled that Arnold originally pointed out that the bone-marrow is essentially a lymphoid structure. This fact has been emphasized by a number of later writers who have been concerned with the myelogenic origin of leukemia. A considerable series of cases has now been reported from various places

which prove beyond question the possibility of a purely myelogenic acute lymphocytic leukemia.

Saxer regards the wandering cell of the tissues as the parent cell of both red and white corpuscles. The production of the corpuscles is brought about by several generations of subdivision and differentiation of the primary cell.

Pappenheim, who believes in the common origin of the red and white cells, bases his conclusions largely on theoretic considerations, as well as on the study of embryonal and adult marrow. He claims to have discovered all kinds of transitional stages between lymphocytes and megalocytes on the one hand, and granular leukocytes on the other. The origin of the different series of cells is the primitive lymphoid cell, from which the differentiated lymphocyte of the circulation is derived and can not be further transformed. From the primitive lymphoid cell, however, may be derived hemoglobiniferous cells as well as the granular leukocytes.

Grawitz insists that the large mononuclear form is the mother cell, and he designates it as an "unripe cell" capable of differentiation into a basophile cell or, by neutrophile transformation, into a neutrophile myelocyte. According to his scheme of blood formation, all of the forms of red and white corpuscles are derived from this original unripe cell. Wolff, who insists that the lymphocytes can not be differentiated from granular cells, in view of the fact that granular lymphocytes have been found by Michaelis and himself, and, further, who asserts that the lymphocytes are actively motile, and that active lymphocytosis occurs, states that the original leukocyte is an "indifferent lymphoid" cell; this, though similar to the ordinary lymphocyte morphologically, is capable of differentiation, and the lymphocyte of the bone-marrow, he states, is distinguishable morphologically from the ordinary lymphocyte. Wolff, however, believes that in post-embryonal life certain parts of the blood-making system have special function; thus the bone-marrow makes granulocytes, the lymph-glands lymphocytes, and the spleen large mononuclear cells, but all these organs contain indifferent lymphoid cells. According to his scheme, all forms of both red and white corpuscles may be derived from the indifferent lymphoid cell.—ED.].

DESCRIPTION AND SIGNIFICANCE OF THE CELL-GRANULES.

In the last ten years histologic, biologic, and clinical investigations have delved deeper and deeper with continually increasing success into the question of the significance of cell-granules. Hematology in particular has come to a series of important conclusions which

could have been reached by no other means. It appears advisable, therefore, to detail the history, the methods, and the results of these investigations.

The honor of first calling attention to the great significance of the granules, and of reaching practical conclusions by a systematic investigation continued through years, belongs incontestably to Ehrlich. It is necessary to emphasize this because Altmann has repeatedly asserted the opposite in spite of express contradication. After Ehrlich had absolutely denied Altmann's pretensions to priority, in a special communication in the year 1891,[1] Altmann, in a second edition of his *Elementarorganismen*, appearing in 1894, repeats that he was first to recognize the specific significance of the granules, and that the few investigators who had observed them, considered them only as special and occasional appearances. In the following, therefore, there will be mentioned a few emphatic points from Ehrlich's work.

One of the first publications on this subject, which appeared in 1876,[2] in other words, ten years before Altmann's work, shows that Ehrlich was even then far beyond considering the granules of the cells as "vereinzelte Erscheinungen," etc. Moreover, only the firm conviction that he was dealing with extremely important biologic elements could cause an investigator to devote ten years of his principal work to this subject.

In the place mentioned one reads: "In the description of cellular pictures the word 'granulated' has been employed since the beginning of histology. This expression is not very felicitous, since many circumstances may produce the appearance of granulation of the protoplasm. For instance, modern methods have shown that many elements, previously described as granular, give this impression only on account of a net-like protoplasmic stroma. It is, moreover, improper to designate as granular those cells in which granular albuminous precipitates arise either spontaneously or by rigor or under the influence of certain reagents (alcohol), since this term must be reserved for intra vitam deposits which are chemically differentiated from the normal albumin of the cell. Only a few of these granules, like fat and pigment, are readily recognized. By far the greater number are little, if at all, characterized by our present methods. The majority of investigators are content, therefore, to determine the presence of the granules in certain cells, and according to whether they were more or less refractive describe them as fat-drops or albumin.

[1] For the history of the granules, see Ehrlich's *Farbenanalytische Untersuchungen*, xii., p. 134.

[2] *Ibid.*, pp. 5 and 6.

"Previous experience, especially with mast-cells, led me to suspect that these granules irresponsive to chemic investigation, would become recognizable on staining—*i. e.*, by their behavior toward certain dyes. Further, I found that these granules could be so characterized, and was able to follow them through different animals and organs. I was likewise able to demonstrate that certain of the granules occurred only in very definite cells, and that they characterized these cells as pigment characterizes pigment-cells—glycogen, cartilage-cells (Neumann), etc. Just as in the differentiation of the proteiform mast-cells, our criterion is the staining of the granulations by dahlia, which is a microchemic reaction, so we succeeded in separating by their staining properties other granular cells, impossible to differentiate morphologically, into several readily defined subclasses. On account of their differential characteristics, I would propose designating these granules *specific granules*.

"The examination was made in the way proposed by Koch, as follows: the fluids (blood) or the parenchyma of an organ (bone-marrow, spleen, etc.) were spread out in the thinnest possible layer on cover-glasses, dried at the room temperature and stained after a varying period. I chose this somewhat rough method with the idea that all substances which, like water or alcohol, could act as solvents, or like osmic acid as an oxidizing agent, should be avoided in the histologic study of new granulations (fearing new chemic combinations), and that one should employ only procedures such as simple drying, which would as far as possible, leave unaltered, the chemic properties."

A further advance in this very difficult subject of histology was possible only through a careful study of staining methods and the relations which exist between chemic constitution and the power of staining. The sharp differentiation of acid, basic and neutral stains, and the corresponding oxyphile, basophile, and neutrophile granulations, undiscovered in all previous work, was the first result of this investigation. It naturally required combinations repeated hundreds of times to produce the *triacid solution*, which, in its original form or slightly modified, continues to play a prominent rôle in histologic study.

The separation of the cell-granules of the blood according to their different chemic affinities furnishes even to-day the most available classification of leukocytes. Ehrlich insisted from the beginning that *different varieties of cells possess different granules* which can be differentiated not only by their behavior to stains, but likewise by their reaction toward solvents.

Exactly in this regard Altmann's method, which makes use of a complicated hardening process and one single stain, is a retrograde

step, since it is apt to conceal the specific peculiarity of the granulation.

A further disadvantage of Altmann's method of hardening is that albuminous substances in the cells are precipitated as round granules which stain under the subsequent treatment. It is therefore exceedingly difficult to differentiate what was preformed and what is artefact. Since the publication of A. Fischer's investigation, in which granular artificial products were experimentally produced by the action of different reagents, doubt has arisen as to the reality of Altmann's pictures. In contrast to this the drying method employed by Ehrlich is absolutely unobjectionable. Granules can not be artificially produced by drying, and the stained pictures correspond exactly with what is seen in the fresh living blood. Moreover, the greatest value of the dry method lies in the fact that the chemic nature of the different granules is preserved, and, therefore, the chemic tests are made on objects almost entirely unchanged.[1]

Another method of studying the nature of the granules depends on the principle of *vital staining*. The first attempts to stain granules in the living animal were incited by Ehrlich's "vital methylene-blue staining," which has attained such great importance, especially in neurology. One of the first publications on this subject was that of O. Schultze, who placed the larvæ of frogs in thin methylene-blue solution, and after a short time found a blue staining of the granules, also of the intestine in particular, of the red blood-corpuscles and other cells. Still this method, as shown by Ehrlich, in his methylene-blue studies, is not entirely unobjectionable inasmuch as the continued action of methylene-blue frequently produces granular precipitates which may be confused with preformed granules. Teichmann's thorough investigations were directed to this point, and he designates the majority of the granules described by Schultze as artefacts.

The most suitable dye for the study of the vital staining of granules is *neutral red*, recommended by Ehrlich, and employed with good results by Przesmycki, Prowazek, S. Mayer, Solger, Friedmann, Pappenheim, and others. This dye, made by O. N. Whitt, from nitrosodimethylanalin and metatoluylendiamin, is the hydrochloric acid salt of a basic dye which dissolves in pure water with a fuchsin-red color, and in weak alkaline solutions—the alkalinity of spring water is sufficient—with a yellowish orange.

Neutral red is characterized by a great affinity for the majority of

[1] Altmann's freezing process corresponds to the requirements demanded by Ehrlich. Still its technical difficulties are so great that it has so far met with no general approval.

granules. Even in certain plant-cells Ehrlich succeeded in demonstrating the granules by means of this stain. Its employment is most simple, namely, in the higher animals by subcutaneous or intravenous injection, or even feeding; while in the case of the larvæ of frogs and invertebrates it is frequently sufficient to allow them to swim in a dilute solution. The stain also succeeds in organs that survive the death of the organism. This is best accomplished by placing small pieces in physiologic salt solution to which a trace of neutral red has been added, and allowing them to remain there for a short time exposed to the open air. When the object is macroscopically red, it is ready for examination.

The best results are naturally obtained in organs which are readily teased—*e. g.*, the eggs of flies and the Malpighian canals of insects. The stain should be so prepared that a very long time is not required for its action, and a very high concentration must likewise be avoided. A dilution of about 1 : 50,000 to 1 : 100,000 is most suitable in order that the nucleus may remain unstained. The endeavor is to obtain pictures in which the granules alone are stained, while protoplasm and nucleus remain unstained. Artefacts can not be entirely excluded; in plant cells containing tannin they are due to the formation and precipitation of tannic acid salts of the dye. In individual cases, however, it is not difficult for the experienced to recognize the artificial products as such. The appearance of the granules, their typical distribution, their likeness to those of neighboring cells, the combination of different methods, the comparison of the same object in pure vital and *survival staining*, render the diagnosis easy and prevent error.

The majority of granules in vertebrates are stained orange-red by the neutral red, corresponding to the faint alkalinity present. Much more rarely granules are seen, which stain a pure fucusin red, and which therefore must possess a faint acid reaction.

As a valuable addition to the neutral red method combination staining is to recommended. Ehrlich employed, for instance, for the larvæ of frogs, a neutral red solution to which a trace of methylene-blue had been added, and found red granules almost exclusively, the granules of the unstriped muscle of the intestine alone staining intensely blue. By the aid of a triple combination Ehrlich obtained further points of differentiation in the living cell-granules. There can be no question that a thorough study of this neutral red method will lead to further important conclusions as to the nature and function of the granules in the problem of cell-life. Even the information gleaned up to the present has furnished definite, well-grounded facts in regard to the biologic significance of the cell-granules.

In his first publication, Ehrlich described the granules as *metabolic products of the cell* deposited in a solid form, some of which were intended as reserve material, others were to be excreted from the cell. Later he rejected this view for a time on account of certain observations in liver-cells, thoroughly described in the well-known work of Frerich (1883, p. 43). Ehrlich demonstrated that in dry preparations of a rabbit's liver which contained considerable glycogen the liver-cells appeared as large polygonal elements of uniform homogeneous brown color limited at the periphery by a thin, sharp, pure yellow membrane. In cells containing less glycogen round pure yellowish particles, evidently of protoplasmic nature, were found deposited in the homogeneous glycogen brown contents of the cell. "On staining, it was seen that the general hyaline part of the cell which contained the glycogen, remained unaffected, while the membrane and the granules present stained with all possible dyes. Moreover, the membrane could be chemically differentiated from the granules in that with eosin-aurantia-indulin-glycerin the membrane stained black, the granules reddish orange."

From these observations Ehrlich then concluded "that in the digesting liver the cells possess a small protoplasmic membrane and homogeneous contents containing glycogen in which the nucleus and the *round* (functionating ?) *granules* of the protoplasm are deposited.

"If we compare these results with those determined by recent investigation, the position of the glycogen is evident. Kupffer found—and this is now acknowledged as a generally applicable law—that the contents of the liver-cells do not represent a microscopically homogeneous substance. In cells in which he preserved life he found near the nucleus two substances readily differentiated from one another, namely, a hyaline ground-substance imbedded in a smaller amount of a finely granular fibrillar substance. Kupffer called the first *paraplasm*, the second *protoplasm*. On heating to about 22° C., an evident though sluggish movement appeared in the network. It can not be doubted that the granular network (the protoplasm) is the more important, and the assumption is warranted that in the granulation of this network the seat of specific cell function will be found. In any case it is advisable that these granules found in the liver-cell in the form of distinct round or oval bodies, which stain yellow with iodin and are likewise readily stained by other methods, be described by a special name, for instance, microsomes (Hanstein)."

It was necessary to quote this previous work so extensively in order to demonstrate that Ehrlich, as far back as 1883, described the granules

as the specific carriers of the cell function, a view which many years later Altmann advocated under the name "bioblastic theory." Moreover, it contradicts Altmann's repeated assertion that he was the first to attribute such importance to these granules.

The significance attributed by Altmann to the granules which he described as "ozonophores" is apparent from his own words (p. 39, last edition, *Die Elementarorganismen*).

"In the ozonophores, therefore, we have elements capable of replacing the living protoplasm, at least as far as its vegetable function is concerned, and of serving as a foundation for the many processes of organic metabolism. Considering again the properties of the ozonophores in brief, they are capable of both reduction and oxidation by means of the transference of oxygen and of thus effecting the decomposition and combination of bodies, without losing their own individuality."

In the meantime Ehrlich had made various observations which did not accord with his earlier hypotheses and Altmann's far-fetched conclusions. Investigations in regard to the oxygen requirements of the organism especially showed him that the "ozonophores" could not be an integral constituent of the cell. In support of this he adduced the fact that cells normally occur in which with our present methods no granules can be found. Finally, a pathologic observation showed it to be impossible that the granules could be the carriers of the cell function. In the examination of a case of pernicious anemia (see *Farbenanalytische Untersuchungen*) Ehrlich found the polynuclear cells of the blood and the bone-marrow, as well as their primary stages, free from neutrophilic granulation. Upon this discovery Ehrlich returned to his original opinion that the granules are secretory products of the cells, and defined his position in the following words:

"If the neutrophile granulations, as Altmann assumes, actually represent elements which furnish the cell with oxygen, such an occurrence as that just described would be impossible for the reason that with the disappearance of the granules the cell would necessarily die; however, from the standpoint of the secretory theory this finding is readily explained; for just as under certain circumstances the fat-cells may lose their contents without dying, the bone-marrow cells may occasionally be unable to form neutrophile granulations when the blood does not deliver the necessary material, and they may consequently be transformed into non-granular cells."

The theory that the granules are peculiar metabolic products of cellular activity is supported by their chemic differences. Ehrlich remarked this especially in the blood-cells, in which the granules can be

differentiated not only by their reaction to stains, but also by their form and solubility.

[As far as this controversy is concerned, it appears that Altmann has consistently defended his original proposition, that the granules are primitive anatomic constituents of the cell, while Ehrlich's view has undergone some change as is here detailed.—ED.]

Moreover, while the majority of granules show a more or less round form, we find them in some species of animals, for instance, birds, characterized by a pronounced crystalline form and marked oxyphilia. Even the substance contained in the mast-cell granulations of some species of animals shows a crystalline shape.

The size of the individual specific granules is definite for every species of animal with the exception of those in the mast-cells. The eosinophile granulations, for instance, attain their greatest size in horses, where true giant forms are seen.

Granular white blood-cells have been demonstrated in the most different species of animals, even the invertebrates, especially the lamellibranchiatæ, the polychetæ, the pedatæ, the tunicatæ, the cephalopodes, as Knoll has shown.

Numerous and accurate investigations have been made especially on the higher vertebrates. There are recognized, for instance, in birds, two oxyphilic granules, one deposited in crystal form, the other in the ordinary granular form. Among the mammalia the majority of animals examined showed a granular polynuclear cell, and very recently Hirschfeld devoted a special investigation to this subject. Among other important details, he found neutrophile granules in the polynuclear cells of all animals examined except the white mouse.

The investigations of Dr. Franz Müller, made some years ago in Ehrlich's laboratory, show that this assertion of Hirschfeld's is not to be relied upon. After many painstaking efforts Müller succeeded in finding a method (which he has described) by means of which numerous though very fine granules were discovered in the polynuclear cells of the mouse. This instance shows that the absence of granules can not be assumed from the failure of the ordinary staining methods. A universal method is no more applicable to all granules than to all varieties of bacteria. Consequently granules consisting of readily soluble substances may apparently disappear under the ordinary triacid method and delude the observer by a homogeneous cell-production.

[It may be asked whether this fact has been sufficiently considered in connection with instances like Ehrlich's case of pernicious anemia in which non-granular polymorphonuclear cells were found.—ED.]

Naturally this explanation does not deny the occurrence of non-granular polynuclear cells in certain species of animals. That granular and non-granular polynuclear cells are found, for instance, in dogs, is granted by Hirschfeld, and he draws from this fact the broadest conclusion as to the significance of the granules. Still, on the ground of Kurloff's work (see p. 73), we must insist that there is no proof that the non-granular polynuclear cells are identical with the granular ones. It has been shown by Kurloff, at least in the case of guinea-pigs' blood, that these two elements are sharply separated from one another and have an entirely different genesis.

An important fact in regard to the nature of the granules is that they are found, in general, in all species of animals only in the cells of the blood which are capable of motility. That a certain nutritive function is therefore to be attributed to the granules, can scarcely be doubted, since it is naturally cells containing considerable reserve matter that would be especially adapted for this purpose. Moreover, the lymphocytes which lack the faculty of emigration are also almost entirely lacking in specific granulations.

A further proof that the granules stand in relation to a specific activity on the part of the cell lies in the fact that a cell invariably contains only one variety of granulation. The contrary assertion, that neutrophile and eosinophile or eosinophile and mast-cell granulations occur in one and the same cell, is denied by Ehrlich on the ground of extensive observations directed especially to this subject. Nor has he ever seen the transition of a pseudo-eosinophile cell of a rabbit into a true eosinophile.[1]

That such a transition does not take place is most readily proved by the fact that the different granulations behave differently to solvents. By the aid of acids, for instance, the pseudo-eosinophile granules may be extracted from the cells, while the eosinophile remain intact and can be stained separately from the pseudo-eosinophiles.

The most evident proof that the neutrophile, eosinophile, and mast-cells are separable from one another by original differences in their

[1] The varied staining of the granules at different stages of development, discussed on p. 87, has given rise to this misunderstanding. How little staining properties alone can be taken as a criterion to determine the chemic identity of granules, is at once evident on considering the granules of other organs. No one would say, for instance, that a liver-, muscle-, or brain-cell could secrete pancreatin simply because with different methods of staining the granules of the pancreas stain similarly to these cells. We wish, therefore, to insist expressly that we assume a similarity of character from the variety of granulation only in the case of the blood-cells which have a comparatively simple function, while we acknowledge that in highly complicated glandular cells which perform different functions simultaneously, several kinds of granules may be present.

protoplasm, of which the granulations represent only one factor, is found in the study of the different forms of leukocytosis. Here we find, as will be more thoroughly discussed in the next chapter, that the neutrophile and eosinophile leukocytes act very differently in regard to chemotactic irritation. The substances which act in a positive or negative chemotactic manner on one group of cells, as a rule, prove indifferent to, or have a reverse action on other groups. In this regard the difference between the mast-cells and the other two varieties is most striking, for, as far as investigations extend, they are not at all influenced by substances acting chemotactically on the neutrophiles or eosinophiles.

Corresponding to the character of the granules as specific secretions of the cell, the different forms must be sharply differentiated from one another in their chemic properties. The granules of the blood-corpuscles appear to be of a relatively simple chemic composition. At least, we have grounds for the assumption that the crystalline granulations usually consist of a single substance which seems to be a relatively simple body, somewhat similar to guanin, fat, melanin, etc. The other granules certainly have a more complex composition, and sometimes consist of a mixture of different chemic substances. The most complicated granules in the blood are undoubtedly the eosinophiles, and, as previously described, they also show a higher histologic structure in that we can differentiate an evident peripheral marginal layer and a central part. We may mention that, according to Barker, the eosinophile granulations seem to contain iron.

The keystone of the hypothesis of the secretory nature of the granules would be furnished only by direct observation of the secretory process itself. Such investigations are naturally extremely difficult, inasmuch as a series of fortunate coincidences would be essential to the study of the steps of the process.

For such investigations the mast-cells are especially adapted, since their specific granules are sharply characterized by a peculiar metachromatic stain and such a marked affinity to basic dyes, that they remain stained even after the preparation has been almost completly decolorized. As a matter of fact, we not infrequently find conditions in the mast-cells attributable only to such secretory processes.

In the first place, we sometimes see the granulations dissolve in the protoplasm, and in this dissolved condition diffuse throughout the nucleus. In place of the colorless nucleus surrounded by the intensely stained metachromatic granulations ordinarily seen in the mast-cell (see p. 68), a markedly stained nucleus, of the same color as the granu-

lations, is found surrounded by a protoplasm which shows only traces of the granules.

The occurrence of a peculiar ring in the mast-cell noted by different observers is still more convincing. Ehrlich first described this area in his book on the oxygen requirement of the organism. A few years ago Unna, unaware of Ehrlich's discovery, described an analogous finding as follows: "With the new mast-cell stain (polychrome methylene-blue, glycerin, ether mixture) the mast-cells were found in a few instances in the same case more than double as large as ordinarily, owing to the staining of a large round area in the center of which lay the well-known mast-cell, consisting of a blue nucleus surrounded by deep-red granulations. Stronger powers showed that although this area was exactly of the same red color as the granulations, it was not granular but finely spongy. We had to do, therefore, with a spongioplasm peculiar to these mast-cells."

The appearance described by Unna in these mast-cells can be produced artificially by leaving the preparations stained with oxonin (the oxygen-containing analogue of thionin) a short time in levulose syrup or in watery glycerin. By this means a portion of the stained mast-cell is dissolved though retained about it. Still since Unna has had extensive experience, especially in regard to mast-cells and their methods of staining, we must assume that the area described by him was preformed and did not arise in the preparation.

We must conclude, therefore, that an analogous process can occur during life, when this area would represent a vital secretion of the specific mast-cell substance.[1]

A discovery made by Prus in the so-called purpura of horses is likewise to be explained as a secretory process of the mast-cells. He described hemorrhagic foci in the intestinal walls containing young mast-cells which showed at their periphery formations which were differentiated by staining from any ordinarily seen in mast-cells, yet from their shape and position it was evident that they had arisen in the mast-cells. Prus, therefore, came to the conclusion "that the degenerating young mast-cells secrete a fluid or half-fluid substance which as a rule coagulates on reaching the surface, though rarely within the cell."

[1] During correction of the proofs the writer obtained information of Calleja's work on the mast-cells, from which it appears that S. Raymon Cajal recognized the halo of the mast-cells and explained it in the way just indicated. Calleja also describes this halo, as well as the methods for demonstrating it (staining with thionin and the preservation of the section in glycerin). Still, from what has been said, the writer can not admit that this method is suitable for the demonstration of the preformed halo.

Moreover, observations have occasionally been made on polynuclear neutrophile and eosinophile cells which indicate that the granular substance may be excreted exteriorly. Hankin, for instance, found in the blood of rabbits in which he had produced an experimental leukocytosis an evident progressive decrease of the (pseudo-) eosinophile granules when he left the preparations some time in the thermostat. Moreover, in cases of suppuration in man, especially in old abscesses (Janowski), we find a diminution of the polynuclear neutrophile granules, even to their entire disappearance, which is to be explained only by the excretion of the granules.

All these facts and considerations lead, therefore, to the conclusion that the wandering cells are generally capable of excreting the granules. This is perhaps one of the most important functions of the polynuclear leukocytes.

LEUKOCYTOSIS.

The problem of leukocytosis is one of the most actively discussed in modern medicine. An exhaustive description of the work devoted to it, the methods employed, and the conclusions, would alone fill a volume, and would far exceed the limits of a treatise on blood diseases. We can, therefore, only mention in brief, the principal views and go into detail only in regard to purely hematologic questions.

Virchow designated as "leukocytosis" the transitory increase of leukocytes in the blood which he demonstrated in a large number of histologic and pathologic conditions. Following him, special attention was paid to its occurrence in infectious diseases, and to these investigations during the last fifteen years we owe the most important conclusions as to the **biologic significance** of this symptom. The greatest credit is due to Metschnikoff for his effective pioneer work in the theory of phagocytosis, and though this theory has been demolished in many of its important details, it incited much of the investigation done on the subject generally.

To indicate Metschnikoff's teaching by a few strokes requires only a paraphrasing of the pregnant word "phagocyte, scavenger cell." This word alone makes the theory evident, namely, that the leukocytes protect the body from injurious micro-organisms by taking them up, and thus preventing further action. The occurrence of an infectious disease, therefore, depends on whether a sufficient number of leukocytes are present in the blood to correspond to the invading bacteria.

This theory of Metschnikoff underwent decided modifications on further investigation. Denys, Buchner, Martin Hahn, Goldscheider and Jacob, Löwy and Richter, and many others have demonstrated that

the most important weapons of the leukocytes are not their pseudopodia, by which they mechanically take up the bacteria, but rather the chemic products ("alexins," Buchner) which they excrete. These excretory products are antitoxic or bactericidal in action, and paralyze the toxins produced by the bacteria, thus rendering the invaders innocuous by the destruction of their weapons, even when they do not destroy the organisms themselves.

The fact that the leukocytes are almost always increased in the blood in bacterial diseases corresponds to the chemic as well as the phagocytic theory of leukocytosis on the principle of *chemotaxis* discovered by Pfeffer. For according to this the bacteria or their metabolic products are capable of attracting by chemic irritation the cells stored in the blood-making organs ("positive chemotaxis"). In cases in which a diminished number of leukocytes is found in the blood, we see the result of a repulsion of the cells, "negative chemotaxis."

On the further experimental investigation of leukocytosis, after learning that it could be produced by the injection of different chemic substances (bacterial proteins, albumoses, organic extracts, etc.), it was found that its explanation on the theory of chemotaxis was by no means complete. Löwit, for instance, showed that on the introduction of these substances two different stages were to be differentiated: First, a stage in which the leukocytes were diminished ("leukopenia," Löwit), this diminution affecting only the polynuclear cells, while the lymphocytes remained normal; following this, a stage in which the white blood-corpuscles were increased, this increase being likewise limited to the polynuclear cells, making a polynuclear leukocytosis. This seemed to indicate that during the first period there is a destruction of white blood-corpuscles, and that it is the soluble products of these which act chemotactically in causing the outwandering of new leukocytes. To this theory new objections arose.

Goldscheider and Jacob especially proved on careful experiment that the transitory leukopenia of the blood is not a true, but only an apparent one, produced by an altered distribution of the white blood-corpuscles within the vessels; and that while the peripheral vessels from which the blood is generally taken, show a diminution of leukocytes, "*hypoleukocytosis*," the capillaries of the internal organs, especially those of the lungs, show an outspoken increase of leukocytes, "*hyperleukocytosis*." Still other important factors speak against the significance attributed by Löwit to the leukopenia. It is *a priori* impossible to understand how different substances which exercise an evident chemotactic effect on the leukocytes in the tube experiment would require under other circum-

stances the previous action of products of leukocytic decomposition. Moreover, general clinical experience is against Löwit's theory, for though hyperleukocytosis is frequently observed in infectious diseases, it is but rarely that a transitory stage of leukopenia is seen.

This contradiction of Löwit's experimental finding is readily explained when we consider how very different an experiment is from a natural disease-process. In the former the animal experimented on is overwhelmed at once by an intravenous injection of the injurious substance, and an intense acute reaction of the vascular system is naturally the result. In the natural infection the poison enters insidiously and increases gradually, and possibly the hypoleukocytosis is for this reason much less frequently seen in the normal course of infectious diseases than in the brusque experiment.

An immense amount of material has been gathered together on the clinical significance of leukocytosis, especially in infectious diseases and their individual stages. Taking from this material pneumonia as the best studied example, we find the constant occurrence of leukocytosis in a typical case to be incontestable. It usually lasts till about the crisis, when the number of leukocytes gradually diminishes to even below the normal. The absence of leukocytosis in severe or fatal cases (Kidodse, Sadler, v. Jaksch, Tschistowitch, Türk, and others) is of special importance.

The observation has likewise been made in many other diseases that hyperleukocytosis is as a rule absent only in severe or otherwise atypical cases. Moreover, several investigators (Löwy and Richter, M. Hahn, Jacob) have been able to show that an artificial hyperleukocytosis influences the course of different infectious diseases favorably. The question how this succeeds in protecting the body is at present actively discussed, and its solution opens up the most difficult problems in biology.

The **morphologic character of leukocytosis** is by no means uniform, and according to the variety of cell increase we must separate different kinds of leukocytosis.

In accordance with the views which have been expressed in preceding sections, we must consider whether those varieties of leukocytes are increased which are capable of independent motility, and of responding to chemotactic irritation by emigration ("active leukocytosis"), or others which possess no such motility, and are, therefore, only passively forced into the circulation ("passive leukocytosis").

The passive form of leukocytosis corresponds to the different forms of lymphemia occurring in the course of leukemia and other diseases. In the section on the Lymph-glands (see p. 85) the writer has thoroughly

described this condition, and has shown that a suppuration consisting of lymph-cells does not exist.

In sharp contrast to this there are specific inflammatory products (pus, exudate) consisting of similar cells for every specific form of active leukocytosis.

Active leukocytoses are divided into the following sub-groups:

a. Polynuclear leukocytoses:

1. Polynuclear neutrophile leukocytosis,
2. Polynuclear eosinophile leukocytosis.

β. Mixed leukocytoses with participation of the granuliferous mononuclear elements, "myelemia."

Polynuclear Neutrophile Leukocytosis.—Among the forms of active leukocytosis, this is by far the most frequent. It may be produced by a large number of very different conditions and influences.

Virchow, the discoverer of leukocytosis, suggested that it is due to irritation of the lymph-glands, which respond "by an increased formation of cells and an enlargement of the follicles, so that after a short time they contain more cells than previously." The enlargement of the lymph-glands is followed by an increased number of lymph-cells in the lymph, and then by an increase of colorless corpuscles in the blood.

This view was necessarily rejected when Ehrlich showed that the leukocytosis was principally due to the entrance into the blood of polynuclear neutrophile cells. Exact estimations were first made by Einhorn under Ehrlich's direction, and these were later confirmed. Corresponding to the exclusive increase of the neutrophile corpuscles, the percentage of lymphocytes is always diminished, frequently to even 2 per cent. or lower; but it must be remembered that the percentage of lymphocytes may be diminished without any alteration in their absolute number. Still it has been proved that in cases of polynuclear leukocytosis there is sometimes a diminution of the absolute number of lymphocytes. Einhorn described such a case, and recently Türk put the matter on a firm basis by a series of absolute estimations.[1]

The eosinophile cells are, as a rule, absolutely diminished in the ordinary polynuclear neutrophile leukocytosis, as shown by Ehrlich in his first communication on this subject. This diminution is frequently marked, sometimes to complete disappearance of these cells.

A very few diseases, however, as will be discussed more in detail in

[1] It is naturally possible for an ordinary leukocytosis to be combined with a lymphemia. In another section it is mentioned (see p. 83) that this coincidence takes place in digestive leukocytoses and in the intestinal diseases of children.

the next section, show, besides the polynuclear neutrophile leukocytosis, an increase in eosinophiles.

Polynuclear neutrophile leukocytoses—the leukocytosis κατ' ἐξοχήν—can be divided clinically into several groups. We distinguish :

Physiologic Leukocytosis.—This occurs in health as the expression of a physiologic change on the part of the organism. In this category belong the digestive leukocytoses, the leukocytosis after bodily effort (Schumburg and Zuntz), after cold baths, and during pregnancy.

Pathologic Leukocytoses.—1. This increase of polynuclear cells occurs in the majority of *infectious processes*, as pneumonia, erysipelas, diphtheria, septic conditions of the most different kinds, parotitis, acute articular rheumatism, etc., and has been designated inflammatory according to the principle "a potiori fit denominatio." A particularly striking position in this regard is taken by uncomplicated typhoid fever and measles, in which the absolute number of white corpuscles is diminished, and especially at the expense of the polynuclear neutrophiles. For the details regarding leukocytosis and its course and subsidence in infectious diseases, we refer to Türk's complete monograph. We will only mention here from Türk's observations that at the termination of the leukocytosis, which occurs at the time of the crisis in diseases ending critically, mononuclear neutrophile cells and irritation forms frequently appear in the blood. In still later stages, when the blood is approaching its normal constitution, we frequently find a gradual increasing and again decreasing number of eosinophiles (Zappert and others). Stienon likewise devoted special attention to the leukocytoses of infectious diseases, and very prettily illustrates them by means of curves.

2. *Toxic leukocytosis* is very frequently found in poisoning with the so-called blood poisons. This important group has not been sufficiently studied. Still we may say in general that the majority of blood poisons like potassium chlorate, the derivatives of phenylhydrazin, pyrodin, and phenacetin, seem to produce, in addition to the destruction of red blood-corpuscles, a considerable increase of leukocytes in man as well as experimentally (Rieder). We have seen marked increase of the white blood-corpuscles in the following conditions: poisoning by arseniuretted hydrogen and by potassium chlorate, in one case of fatal hemoglobinuria (sulphonal poisoning?)[1] and after a protracted chloroform narcosis.

3. The leukocytosis which accompanies acute and chronic anemic conditions, especially the post-hemorrhagic. (Further details in the Special Part of this volume.)

[1] The specimens of this case we owe to the kindness of Prof. Stern (Breslau).

4. *Cachectic leukocytosis* of malignant tumors, phthisis, etc.[1]

To go more into detail in regard to the particular *clinical significance* of the blood-picture in different diseases would lead too far, and the writer refers therefore to the splendid monograph of Rieder and the treatises of Zappert and Türk. Only the most important points will be mentioned in this place.

(*a*) The *differential diagnostic* significance of a leukopenia in typhoid fever in contrast to the other infectious diseases, and of measles in contrast to scarlet fever.

(*b*) The *prognostic significance* of the number of white blood-corpuscles, for instance, the absence of leukocytosis, influences the prognosis of pneumonia unfavorably (Kikodse, and others), and according to C. S. Engel, the appearance of numerous myelocytes during diphtheria is ominous (see p. 69).

Taking up in brief the manner of *origin* of polynuclear neutrophile leukocytosis, we can appeal to what has been said in another section on the function of the bone-marrow.

On the ground of Kurloff's investigations, Ehrlich expressed the following views (*Ueber schwere anämische Zustände*, 1892): "The bone-marrow is a breeding-place in which immense numbers of polynuclear cells are formed from mononuclear. These polynuclear cells show, above all other elements, the power of emigration. This power becomes immediately evident when substances chemotactic to the white elements circulate in the blood. This explains why so many substances, especially the bacterial proteids designated by Buchner as leukocyte irritants, can produce a rapid appearance of immense numbers of leukocytes. With Kurloff, therefore, I regard leukocytosis as a function of the bone-marrow."

The contradictory behavior of the eosinophiles and neutrophiles is of considerable theoretic interest. At the height of ordinary leukocytosis the number of eosinophiles often diminishes even to their absolute disappearance, while with its decline they appear again in normal numbers. This would indicate that eosinophiles and neutrophiles react to a certain extent in opposite ways to irritative substances. It appears that the ordinary metabolic products of bacteria occurring in human diseases

[1] We can not, however, reckon the so-called agonal leukocytosis in this category, since we do not consider it a genuine leukocytosis, but only the indication of a depressed circulation caused by the agonal condition. During this condition, especially in the peripheral parts of the body which are employed as a rule for the blood examination, the white blood-corpuscles adhere to the vessel-walls in such a way as to produce the picture of leukocytosis.

which act in a positively chemotactic manner on the polynuclear neutrophiles, are negatively chemotactic for the eosinophiles, and *vice versa*.[1]

The explanation of the different clinical forms of leukocytosis can readily be drawn from these considerations. The physiologic and inflammatory leukocytoses are to be referred exclusively to the principle of chemotaxis. In the other forms other factors play a more or less conspicuous rôle; for instance, an increased activity of the bone-marrow or a widespread transformation of fatty into red marrow, causing marked increase in cell-formation.

Polynuclear Eosinophile Leukocytosis (including the Mast-cells).—The knowledge of eosinophile leukocytosis is comparatively recent. After Ehrlich had demonstrated the constant increase of eosinophile cells in leukemia, a considerable period intervened before eosinophilia was found in other diseases. The first investigations in this line were made by Gollasch at the instigation of Friedrich Müller, on the blood of asthmatics, in which he was able to demonstrate a considerable increase in the eosinophile cells. Following these we have the investigations of H. F. Müller and Rieder, who discovered the frequency of eosinophilia in children as well as its occurrence in chronic tumors of the spleen. Still later came the well-known work of Edm. Neusser, who showed a striking increase of the oxyphilic elements in pemphigus, and almost simultaneously the analogous observations of Canon in chronic skin diseases. Among the numerous other works on this subject, we will refer only to the comprehensive treatise of Zappert. This monograph, which contains a collection of the material to date, as well as numerous observations indispensable to every investigator who occupies himself with this subject, indicates the immense general and special significance of the eosinophile cells from a clinical point of view.

By *eosinophilia* is understood an exclusive increase of the polynuclear eosinophiles in the blood. A confusion of this form of leukocytosis with leukemia is quite impossible, since a whole series of other characteristics are necessary to the diagnosis of the latter, as will be shown in the following section. Moreover, it is not allowable, as has been sometimes done, to regard the presence of mononuclear eosinophile cells as an absolute proof of leukemia, since they are found in isolated cases of ordinary leukocytosis.

[1] It is also of interest to note the behavior of eosinophiles in the massive form of leukocytosis, namely, lymphemia. That lymphemia and eosinophilia ought readily to combine is evident *a priori*. According to C. S. Engel, a simultaneous increase of lymphocytes and eosinophile cells is found in congenital syphilis of children. It is very likely that the lymphocytosis in these cases is to be referred to the alterations in the lymph-glands, and the eosinophilia to specific chemotaxis.

The increase of eosinophile cells is not only relative, but also absolute. The percentage, which normally amounts to 2 to 4 per cent. of all leukocytes, increases in eosinophilia to 16, 20, 30 per cent., and more; in fact, in one case Grawitz found as many as 90 per cent.

[The investigations of Zappert in particular have furnished useful data regarding the absolute number of the eosinophiles. These investigations were made by a method especially devised by Zappert for the purpose.—Ed.] He found as the lowest normal number 50 to 100 per c.mm., as an average 100 to 200, as a high normal 200 to 250. The largest absolute number which he found was 29,000 per c.mm. in a case of leukemia, the highest number in a simple eosinophilic leukocytosis was 4800 in a case of pemphigus. Reinbach found once about 60,000 eosinophile cells per c.mm. in a case of lymphosarcoma colli with metastases to the bone-marrow.

A polynuclear eosinophile leukocytosis, apart from that observed in healthy children, is found in many conditions, and for the sake of clearness the condition may be divided into several groups:

1. *The Eosinophilia of Bronchial Asthma.*—A considerable increase of the eosinophile cells in the blood up to 10 and 20 per cent. and over was regularly found in this disease, first by Gollasch, later by many other investigators (for the clinical course of eosinophilia in asthma, see below).

2. *The Eosinophilia of Pemphigus.*—Neusser was the first to report in several cases of pemphigus an extremely marked, almost a characteristic, eosinophilia. This interesting observation has been confirmed by different persons, especially by Zappert, who once found 4800 oxyphiles per c.mm.

3. *The Eosinophilia of Acute and Chronic Skin Diseases.*—Canon was the first to observe an increase of the eosinophile cells, even to 17 per cent., in a large number of skin diseases, especially prurigo and psoriasis. Canon's statement, that the increase of eosinophile elements seems to depend less on the variety of the disease or its local intensity than on the extent of the process, is worthy of notice. In one case of acute widespread urticaria, A. Lazarus found the eosinophiles increased to 60 per cent.; after the course of several days the number returned to the normal.

4. *The Eosinophilia of Helminthiasis.*—The first observations of this condition were those of Müller and Rieder, who found a pretty high grade of eosinophilia (8.2 and 9.7 per cent.) in two men suffering from Ankylostomum duodenale. Shortly after them Zappert reported an increase up to 17 per cent. in two cases of the same disease, and at the

same time recorded the presence of Charcot's crystals in the feces. In a third case of ankylostomiasis Zappert found neither an increase of eosinophiles in the blood nor crystals in the feces. At about the same time Seige confirmed these observations.

A thorough investigation of this important subject was suggested by Leichtenstern, under whose direction Bucklers determined the interesting fact that eosinophilia was not confined to ankylostomiasis, but that all the varieties of worm diseases in the Cologne Hospital, from the comparatively harmless oxyuris to the pernicious ankylostomum, showed an increase of eosinophiles in the blood, often reaching a high degree.[1] Buckler reports cases of oxyurides with 16 per cent. of eosinophiles, of ascarides with 19 per cent., and the writer learned from a private communication of Prof. Leichtenstern, that he found in one case of ankylostomiasis 72 per cent., and in one case of Tænia mediocanellata 34 per cent.

It is especially noteworthy that Leichtenstern found numerous eosinophile cells in the blood, particularly in those cases which showed large numbers of Charcot's crystals in the feces. Since eosinophiles and Charcot's crystals are frequently associated elsewhere—*e. g.*, in bronchial asthma, in nasal polyps, in myelemic blood and bone-marrow—Leichtenstern's conjecture is justified, that eosinophile cells are to be found in the intestinal mucus in ankylostomiasis. Positive observations in relation to this have not been reported.

The further interesting discovery has been communicated by T. R. Brown, working under the direction of Thayer, that in trichinosis a large relative increase of oxyphiles in the blood up to 68 per cent. constantly takes place. The absolute numbers were likewise markedly increased, and reached figures—*e. g.*, 20,400—which are not frequent, even in leukemia.

Brown considers this striking symptom as pathognomonic of trichinosis, and he was able later to make a correct diagnosis of trichinosis in a clinically obscure case from the marked eosinophilia.

[Da Costa[2] collected 18 cases of trichinosis, reported from 1897 to 1901, in all of which notable degrees of eosinophilia were observed. In a case of his own, however, repeated examinations failed to disclose any increase in the percentage of the cells in the blood, the differential count being small lymphocytes, 36.7 per cent.; large lymphocytes and transitional cells, 6.5 per cent.; polymorphonuclear neutrophiles, 56.1 per cent.; eosinophiles, 0.5 per cent.; myelocytes, 0.2 per cent. The

[1] In his monograph on bothriocephalus anemia, Schaumann asserts that he found eosinophilia in but a few cases of this disease.

[2] *Clinical Hematology*, 1901.

lesions in this case were marked, involving the greater part of the right lower extremity from the calf to the thigh, and excised parts of the muscle contained abundant trichinæ and were rich in eosinophiles. He suggests that the absence of eosinophilia in such cases may be due to an overwhelming dosage of toxin and a stifling of the function of the bone-marrow.

In an imperfectly reported case Howard[1] also records the absence of eosinophilia.

Blumer and Neumann,[2] in reporting an epidemic in which they studied 9 cases, suggest that the degree of eosinophilia is an index to the severity of the parasitic invasion.—ED.]

[W. W. Kerr[3] found marked eosinophilia in 2 cases of trichinosis. The writer could find no evidence in the muscles of a transition of polymorphonuclear cells to eosinophiles. The excess of eosinophiles in the areas surrounding the parasite he believes to be due to a chemotactic and phagocytic process.

Among others who have reported cases of eosinophilia associated with trichinosis are: Gwyn, Stump, Brooks, Kinnicutt, Gordinier, and Cabot. Recently Schleif[4] has reported an extensive epidemic, including 30 severe and many mild cases. Of 64 cases examined, eosinophilia was found in 62. The 2 not showing eosinophilia were doubtful cases. During convalescence there are a decided lymphocytosis and a flooding of the blood with blood-plates, which he believes originate in the eosinophile granules. F. R. Gould,[5] in discussing 6 cases without eosinophilia, notes that a considerable time had elapsed in 4 of these cases from the beginning of the disease to the time of the blood examination. In the other 2 of the 6 cases the trichinæ were well encapsulated in one and calcified in the other. He concludes that an early examination would probably have shown eosinophilia in all.—ED.]

5. *Post-febrile Form of Eosinophilia* (*following various infectious diseases*).—In the section on polynuclear neutrophile leukocytosis it was stated that at the height of the majority of acute infectious diseases, with the single exception of scarlet fever, there is a relative diminution of eosinophiles, or even a complete disappearance of these cells. In the post-febrile period there are frequently found an increase of eosinophiles and sometimes an outspoken eosinophilia, though as a rule the increase is moderate. Türk found in pneumonia a post-critical

[1] *Phila. Med. Jour.*, 1899. [2] *Amer. Jour. Med. Sci.*, 1900.
[3] *Phila. Med. Jour.*, August 25, 1900.
[4] *Deutsch. Arch. f. klin. Med.*, Bd. lxxx., H. 1 u. 2.
[5] *Amer. Med*, September 26, 1903.

eosinophilia of 5.67 per cent. (absolute number 430) following acute articular rheumatism, 9.37 per cent. (absolute number 970); Zappert in malaria one day after the last paroxysm, 20.34 per cent. (1486 per c.mm.).

With Zappert we group the eosinophilia observed after tuberculin injections in this category of post-febrile leukocytoses, for this appears only after marked elevations of temperature. In fact, during the stage of febrile reaction the number of eosinophile cells sinks, but rises again after the decline of the fever. This increase may be considerable. In one case of Zappert's the number of oxyphiles increased to 26.9 per cent.; in another case he found 3220 per c.mm. In one case of Grawitz's the eosinophilia was extraordinary. In this the most marked alteration of the blood was found about three weeks after the discontinuance of the tuberculin injections, which altogether numbered eight (from 5 mg. to 38 mg.). The examination showed 4,000,000 red corpuscles, and 45,000 white corpuscles per c.mm. Among the latter there were 10 eosinophiles to 1 other white cell. The absolute number of eosinophiles amounted to 41,000 per c.mm., the other cells making up the remaining 4000. Since these consisted of polynuclear cells, lymphocytes, and others, it is evident that the polynuclear neutrophiles were greatly diminished, not only relatively, but also absolutely, making the case exactly the opposite to the ordinary leukocytoses, especially those of the infectious variety.

6. *The Eosinophilia of Malignant Tumors.*—An increase of eosinophile cells has been observed by different investigators in tumor cachexias. This does not, however, exceed a moderate grade, about 7 to 10 per cent. In 40 such cases Reinbach found the eosinophiles increased only four times, namely, in one case of sarcoma antebrachii (7. 8 per cent), sarcoma cruris (8.4 per cent.), tumor malignans abdominis (11.6 per cent.), and lymphosarcoma colli with metastases to the bone-marrow in which an unparalleled increase of the white blood-corpuscles, and especially of the eosinophiles, took place. The absolute number of the latter on one day amounted to 60,000, an increase of 300 times the normal and a number never equalled in any condition other than leukemia.

7. *Compensatory Eosinophilia (after Extirpation of the Spleen).*—This form was thoroughly discussed in the chapter on the function of the spleen, where it was also stated that the increase of eosinophiles found in chronic splenic tumors by Rieder, Weiss, and others, must be referred to disappearance of the splenic function.

8. *Medicinal Eosinophilia.*—Of this condition there is only one

single observation, that of v. Noorden. He found an eosinophilia up to 9 per cent. in two chlorotic girls after the internal administration of camphor. Other patients manifested no such symptom, but it is not unlikely that special investigations into the question of medicinal eosinophilia will reveal many interesting facts.

Different theories have been offered by various writers in relation to **the origin of polynuclear eosinophile leukocytosis.** These it is intended to discuss critically.

A frequently quoted explanation is that of Müller and Rieder. In opposition to Ehrlich, these writers do not regard the eosinophile cells as of bone-marrow origin, but assume that they are transformed within the circulation from the finely granulated cells. This process of development appears improbable for many reasons. Since the polynuclear neutrophile cells circulating in the blood are all under the same conditions of nutrition, it is impossible to understand why only a comparatively small number of them should undergo this transformation, and why in inflammatory leukocytosis, in which the number of polynuclear cells is so greatly increased, their maturation into eosinophiles should be entirely interrupted.

Moreover, the fact that a transition of neutrophile cells into oxyphiles is never observed in the blood, speaks decidedly against the Rieder-Müller hypothesis. If this hypothesis were correct, transition-forms should be found in every normal blood. Rieder and Müller have evidently seen no such forms, otherwise they would not be obliged to depend on Max Schultze's observation. As high as Max Schultze's authority is in morphologic matters, it can not remain unquestioned in the case of histochemic questions which require other experience than that of a morphologist for their solution.

In the further exposition of their theory, and in direct opposition to Ehrlich, Müller and Rieder assume that the eosinophile cells of the bone-marrow "do not represent newly formed elements, but rather a storing up of old ones. The bone-marrow, therefore, as far as the coarsely granular cells are concerned, must be regarded as a storehouse in which they are made to serve purposes yet unknown."

These writers base their theory principally on the fact that the majority of eosinophiles in the bone-marrow are mononuclear, while those of normal blood possess a polymorphous nucleus. Müller and Rieder themselves should have seen the evident objection, namely, that the nuclear conditions of the neutrophile cells are exactly the same as those of the eosinophiles. They would then have been forced to assume that the most important blood-making organ is not the cradle,

but the grave of the blood-cells. The simplest explanation, and one based on histologic observation, is that the mononuclear eosinophiles in the bone-marrow progressively develop to polynuclear, and that only the latter have the faculty of emigration by which they enter the blood. As this view has been repudiated by the very great majority of writers since Ehrlich's paper, "Ueber schwere anaemische Zustände," the author will content himself with these objections, even though the theory has lately obtained new advocates—*e.g.*, Lenhartz. It may be added that H. F. Müller himself, in a paper on bronchial asthma (1893), takes a standpoint different from his earlier one and approaching somewhat that of Ehrlich.

The origin of the polynuclear eosinophilia is made most evident by an experiment of E. Neusser's. He found in a case of pemphigus, the blood of which showed a considerable increase of eosinophiles, that the contents of the pemphigus vesicle consisted almost exclusively of eosinophiles. Neusser then produced by a vesicant a non-specific inflammatory vesicle on the skin, and found that the cellular elements in it consisted entirely of polynuclear neutrophile pus-cells similar to those seen in ordinary inflammations.

Analogous conditions occurring spontaneously were demonstrated by Leredde and Perrin in Duhring's disease. The vesicles associated with this disease, as long as their contents were clear, contained only polynuclear eosinophile cells ; but in a later stage, when bacteria had forced their way into the vesicles, neutrophile cells exclusively were present.

Neusser's experiment and Leredde-Perrin's observation can only be explained according to modern theories of suppuration by assuming, as has previously been insisted, that the eosinophiles and neutrophiles react to different chemotactic irritations. The eosinophiles, therefore, wander only to places which possess a substance specifically chemotactic for them. In this way all the known experiments and clinical observations on eosinophilia can be explained. Neusser's experiment, for instance, may be interpreted as follows: In the pemphigus vesicle a substance is present which acts chemotactically on the eosinophiles; these cells present normally in the blood wander out and produce an eosinophile suppuration. If the disease remains of slight extent, this concludes the process; but if it becomes widely distributed, a very different picture develops. Under these circumstances by resorption and diffusion large amounts of the specific agent enter the blood and exercise a chemotactic effect on the physiologic storehouse of eosinophiles, namely, the bone-marrow, with the result that a more or less marked increase of eosinophiles is produced in the blood. Following

this according to general biologic principles, the bone-marrow is excited by the increased demand to increased new formation, and thereby continues capable of preserving the eosinophiles even on long duration of the disease.

A corresponding explanation is applicable to other clinical facts. In the case of Gollasch's discovery, that the sputum of asthmatics contains, in addition to Charcot-Leyden crystals, almost exclusively eosinophile cells, it must be assumed that a substance chemotactic for the eosinophile cells exists within the bronchial tree. Moreover, the close connection, according to many reports, between the severity of the disease and the eosinophiles, would support this. v. Noorden, for instance, reports that the eosinophile cells are more numerous at a time almost synchronous with the asthmatic attack, than at other times. They were especially numerous when paroxysms took place several days in succession. That the increase of the eosinophile cells is dependent on the attack, and is not the expression of a persistent constitutional anomaly, is evident from a case of v. Noorden's which showed during the paroxysm 25 per cent. of eosinophiles, and several days later only a single eosinophile cell in twelve cover-glass specimens; in other words, a diminution in number.

The observations made by Canon on skin diseases are very similar in that the general intensity of the disease appeared to stimulate the eosinophilia less than its local spread; in other words, the factor directly influencing the amount of the specific agent that enters the blood.

In additon to the Müller-Rieder and the chemotactic theory of eosinophile leukocytosis, a third appeared which may be briefly designated as the hypothesis of local origin of the eosinophiles. Especially in relation to asthma, A. Schmidt proposed the question, "whether with the enormous number of eosinophile cells in this disease a local formation along the respiratory tract is not more probable than their origin from the blood. As a matter of fact, the increase of eosinophile cells in the blood of asthmatics may readily be regarded as a secondary phenomenon." This view, advocated also by other writers, is supported by the following facts and considerations:

1. In various diseases of the nose, especially mucous polyps and hyperplasias of the mucous membrane (Leyden, Benno, Lewy, and others) enormous numbers of eosinophile cells are found in the tissues while they are apparently not increased in the blood. This argument is readily met by the chemotactic theory. For if substances are present in these localities which act chemotactically on the eosinophiles, a considerable accumulation may naturally take place in the course of time

without the blood showing any deviation from the normal. Were this not true, the conclusion would follow from Neumann's experiment in lymphatic leukemia, that the polynuclear cells originated in the tissues, for in that instance the artificially produced suppuration consisted only of polynuclear neutrophiles, although these were present in the blood in but minimal numbers. [Weiss maintained that eosinophiles have a local origin from absorption by the polynuclear cells of derivatives of hemoglobin which become deposited as eosinophile granules. His opinions were based on a case of hemorrhagic pleural effusion in the blood of which 40 per cent. of eosinophile cells were found, while in the exudate 76 per cent. of such cells were found. Several other authors have reported observations of a very similar character.—Ed.]

2. Adolf Schmidt proposed a reverse argument in that he showed that the sputum of patients with myelogenic leukemia contained no more eosinophile cells than are ordinarily found in the bronchial secretion, although the blood was extremely rich in them. Still, from the writer's point of view this observation furnishes no support for the hypothesis of local origin, but is, on the contrary, an argument that it is not the larger or smaller number of eosinophile cells in the blood which determines their outwandering, but only the presence of specific chemotactic substance. From the author's observations on leukocytosis in infectious diseases and on the morphology of ordinary pus, it is seen that the bacterial chemotactic substances act rather negatively than positively on the eosinophile cells, and it corresponds only to general experience when ordinary sputum contains no more eosinophile cells in spite of a high degree of eosinophilia in the blood. This is in complete accord with Neusser's pemphigus experiment, in which the specific disease called forth an eosinophilia, while artificially produced suppuration called forth only neutrophile cells. Further, an analogous experiment of Schmidt may be quoted. He found in the sputum of an asthmatic case many eosinophile cells, but in an artificial suppuration of the skin only neutrophile cells.

It is seen then that the principal grounds on which the advocates of the theory of local origin based their theory are unable to withstand the objections raised from the standpoint of chemotaxis. Moreover, histologic or experimental proof of this theory has not been brought forward in spite of numerous investigations in this direction. Still, it may not be amiss to examine closely the possibilities of a local origin of eosinophiles.

In the first place, the eosinophile cells may arise from a progresssve metamorphosis of the normal connective-tissue cells. The possibility

of this is evident from the local origin of the mast-cells. Ehrlich and his school have always considered that the latter arose by a transformation of preformed connective-tissue cells,[1] but that this is applicable to the eosinophile cells has never been proved. In the second place, it is conceivable that isolated eosinophile cells preformed in the tissue rapidly increase and so produce the local accumulation. The proof of this would be the discovery of numerous mitoses, but thus far no karyokinetic figures have been found, though A. Schmidt directed especial attention to them in searching for support of this theory. A third possibility would be their direct derivation from neutrophile cells in the way of maturation. This assumption, too, must be considered weak, since the requirement necessary for its foundation, namely, the proof of corresponding transitional stages, has never been fulfilled.

By way of induction, therefore, the conclusion is arrived at that there can scarcely be any question of a local origin of eosinophile cells. The writer's position is, moreover, strengthened when the behavior of the mast-cells which are closely allied to the eosinophiles, and are practically differentiated from them only by the granulations, is compared. Like the eosinophiles, the mast-cells are a normal constituent of bone-marrow, and occur regularly even though in very small number—according to Canon, 0.28 per cent. of the leukocytes—in normal blood. It is known that mast-cells are formed locally wherever nourishment of the connective tissue occurs—*e. g.*, in chronic diseases of the skin, elephantiasis, and brown induration of the lungs. Moreover, the requirements presumed in the case of the eosinophile cells by the advocates of their local origin are actually realized in the case of the mast-cells. It is, therefore, to be expected that an increase of mast-cells in the blood in the condition described above, or in certain inflammations, would be no rare occurrence. With this in mind, Ehrlich twenty years ago carefully examined the sputum in cases of emphysema and brown induration of the lungs for mast-cells, but without result. Moreover, Canon's examinations of the blood were likewise practically negative. Canon failed to find mast-cells in nine out of twenty-two healthy persons; in the others he found an average of 0.47 per cent. and a maximum of 0.89 per cent. A slight increase only was suggested in several cases of skin diseases which showed an average of 0.58 per cent.; in other words, a number which can be frequently found in health. A mast-cell leukocytosis similar to the eosinophile or neutro-

[1] This theory has lately received striking confirmation by Bäumer's very interesting experiment on himself. After a continuous irritation with urtica urens he obtained in four days a considerable increase of mast-cells at the irritated spot on the skin.

phile leukocytosis was found neither by Canon nor by other observers. Yet in myelogenic leukemia the mast-cells undergo a considerable increase, the number sometimes reaching or even exceeding that of the eosinophiles. Consequently one is not likely to err when regarding the mast-cells of the blood as originating exclusively in the bone-marrow, and not in the connective tissue, even when they are greatly increased in the latter place.[1]

The author believes that he has shown in the preceding that the proofs brought forward in support of the local origin of the eosinophile cells do not stand the tests. The problem is now to show that the accumulation of eosinophile cells in the organs and secretions can be explained by their emigration from the blood.

The demonstration of this problem presents many difficulties, inasmuch as eosinophile cells are found normally in many localities, so that one is unable to follow the steps of a morbid process, but is concerned with completed conditions. The problem will be much easier if eosinophile cells are studied in organs normally free from them. So far there is only one observation of this sort, which was made a short time ago by Michaelis, in Hertwig's Institute. Michaelis found that when lactation was interrupted in nursing guinea-pigs numerous eosinophile cells collected in the course of a few days in the mammary glands, though not in the lumen of the milk-ducts. These eosinophile cells were exclusively polynuclear; and since they corresponded to those of the blood, they must be looked on as having immigrated. This phenomenon can be explained according to modern views, by assuming that the mammary gland under certain circumstances possesses a "secretio interna" containing a substance which increases abnormally when the "secretio externa"—*i. e.*, the production of milk—is disturbed. Thus also is explained the fact that in Michaelis's experiment no eosinophile cells were found in the specific secretion of the gland.[2]

Corresponding observations have also been made in pathologic

[1] The fact that no one has yet met with a pronounced basophile leukocytosis is explained by the assumption that the substance which acts chemotactically on the mast-cells is very rarely elaborated in the body, even much more rarely than the corresponding eosinophilic substance. Diseased conditions in which the substance specific for the mast-cells is present, may show a mast-cell suppuration or a mast-cell leukocytosis. The greatest interest in this connection was aroused by an observation of Albert Neisser's, who (according to a private communication) encountered among a very great number of cases, an instance of gonorrhea in which the purulent secretion consisted exclusively of mast-cells.

[2] Analogous observations on mast-cells were recently published by Unger in connection with the human mammary gland. He observed under the influence of a stagnation of milk a considerable invasion of the typical mast-cells into the glandular tissue.

organs. They were first brought to light in the fundamental work of Goldmann, who found in malignant lymphoma a considerable collection of eosinophile cells within the tumor, and demonstrated anatomically that they had emigrated from the vascular system. He concluded that they were attracted by the action of certain chemotactic substances. Moreover, he and later Kanter reasoned that they were not products of an ordinary inflammation in this instance, since they are wanting in a large number of other diseases of the lymph-glands, particularly tuberculosis. In a similar way Leredde and Perrin, in their investigations of Duhring's disease, showed that the eosinophile cells found in large numbers in the cutaneous tissue apart from the vesicles, have their origin in an outwandering from the circulation.

From a number of different facts, therefore, it is evident that the eosinophile cells occurring in the tissue are not formed there, but have emigrated from the circulation. It is easy to understand how this picture may not be so definite in all cases, for, as has been pointed out in the case of ordinary neutrophile polynuclear cells, the eosinophile polynuclear cells may be transformed into mononuclears, and may be even stationary or approach the character of fixed connective-tissue cells. Such occurrences may readily induce the false conclusion that the reverse method of nuclear transformation is taking place—*i. e.*, a progressive development of eosinophile polynuclear cells from mononuclear.

In harmony with the opinion of Goldmann, Jadassohn, and H. F. Müller, the author finds an explanation for all these facts only in the assumption that the eosinophile cells follow specific chemotactic irritants. This hypothesis readily explains eosinophile leukocytosis, the occurrence of eosinophiles in exudates and secretions, and their local accumulation.

Regarding the nature of these active chemotactic substances, so far only conjectures are permissible. From a clinical standpoint the only thing that has been learned, and which has been mentioned before, is that the ordinary metabolic products of bacteria repel the eosinophile cells.

The contradictory behavior of eosinophiles and neutrophiles is beautifully illustrated by a case, for the knowledge of which the writer is indebted to the kindness of Prof. Leichtenstern:

"In a severely anemic, almost moribund case of ankylostomiasis, 72 per cent. of eosinophile cells were found in the blood in 1897. The patient then acquired a croupous pneumonia, during the acme of which the number of eosinophiles sank from 6 to 7 per cent., rising again to 54 per cent. after

the course of the pneumonia. After the removal of the worms the number fell at once to 11 per cent. In the year 1898, when the ankylostomata were very few and Charcot's crystals were no longer present in the feces, the number of eosinophiles amounted to 7 per cent."

The question as to what cells by their destruction elaborate the chemotactic substance, is extremely important, though it can not be determined with certainty from the material at hand. It does not appear to be the ordinary pus-cells or the lymphocytes, while many observations support the theory that it may be the epithelial and epithelioid cells. This would explain the frequent occurrence of eosinophilia in all sorts of skin diseases, as well as the local accumulations in all atrophic conditions of the stomach, intestinal and bronchial mucous membrane, and in the vicinity of carcinomata. A further support for this view is found in the fact that the eosinophile cells in bronchitis and asthma are the more numerous the less purulent the secretion. Noteworthy too is an observation of Jadassohn's, according to which numerous eosinophile cells were found in a lupous patch after an injection of tuberculin. In this case the substances capable of acting chemotactically on the eosinophiles must have originated from the destruction by the tuberculin of epithelioid cells in the lesion whence they entered the blood. In other cases, as, for instance, nasal polyps, the mucin or the mucin-like bodies must be considered chemotactic. The direct cause, therefore, in the majority of cases of eosinophilia seems to lie in the products resulting from a destruction of tissue.

On the other hand, it is not to be doubted that foreign substances circulating in the body may be positively chemotactic for the eosinophile cells.[1] As an example of this may be mentioned the marked eosinophilia seen in different forms of helminthiasis. Formerly the effect of helminthes was considered purely local, but now the view is steadily gaining ground that they also produce poisons. Linstow, for instance, insists that the general typhoid symptoms of trichinosis, and the fatty degeneration of the liver and kidneys, in other words, of organs in which trichinæ do not occur, make the assumption of a toxin necessary. In several varieties of ankylostomiasis evident signs of the production of a poison are also found. In Husemann's article on "Animal Poisons" (*Eulenburg's Realencyklopädie*, 1897) we are informed that similarly to Ankylostomum duodenale, which produces the well-known

[1] A very interesting observation of Goldmann's deserves mention here. Goldmann observed in preparations of pancreas of Proteus sanguineus, in which parasites were found, that the eosinophile cells were markedly increased in the neighborhood of the capsulated parasites, while they were sought in vain farther away.

severe anemia of man, Ankylostomum trigonocephalum in dogs, and Ankylostomum perniciosum in tigers, produce general effects.

A definite toxin is likewise generally attributed to Bothriocephalus latus, and even the ordinary tapeworms seem to be occasionally responsible for lesions apparently referable to a toxin (Peiper).

Observations show that tapeworms not only take up nutritive material, but also excrete substances which may be absorbed by the intestine of the host, and which are capable of causing wide-reaching results. According to Leichtenstern, one expression of this action is the eosinophilia of the blood. The substance that is chemotactic for the eosinophile cells, for many reasons seems to be different from the substance that produces the anemia; for instance, the absence of eosinophilia in bothriocephalus anemia (Schauman). Still the substance producing the eosinophilia is undoubtedly more generally distributed than that producing the anemia.

Leukemia ("Mixed Leukocytosis").—In spite of the great progress of hematology in the last ten years, considerable of which has been in the realm of leukemia, the literature shows, even in fundamental matters, much that is obscure and unintelligible. This is true especially of the differentiation of the different forms of leukemia.

Though from a purely clinical standpoint a lymphatic, lienal, lienomedullary, and a pure medullary (myelogenic) form of leukemia are differentiated, these are characterized by purely external phenomena which hematology can not follow.

Neumann first demonstrated that the lymphoid growth in lymphatic leukemia is not limited to the lymph-glands, but may be found too in the spleen and bone-marrow. This hyperplastic process may produce a considerable enlargement of the spleen without any alteration in the specific character of the leukemic process or of the blood-finding. In spite of the splenic tumor, then, one has to do with a pure lymphatic leukemia, although such a case would be designated clinically as lymphatic lienal leukemia. The indefiniteness and incorrectness of such a designation are most clearly shown in another form of leukemic metastasis. The liver, for instance, may manifest a considerable increase in size in lymphatic leukemia, due to a lymphoma formation, and following out the previous rule it should be described as a "lymphatic-hepatic form" of leukemia. In fact, this designation would be by no means so confusing as that of lymphatic lienal, for no one could conceive that liver-cells occurred in the blood, while the last-mentioned term leads to no other conclusion than that specific splenic cells participate in the blood-picture.

Further, the assumption of a pure lienal form of leukemia is proved entirely unjustifiable by hematologic investigation. After what has been said on the physiologic participation of the spleen in the formation of blood, the probability of a blood-change, attributable exclusively to disease of the spleen, is almost beyond conception. Moreover, pathology confirms this view; at least Ehrlich, in a very large number of cases, has never succeeded in demonstrating from blood examinations a purely lienal form.[1]

The conditions of myelogenic leukemia are similar, inasmuch as the spleen or lymph-glands may show metastatic foci of myeloid tissue. Since the growth of myeloid tissue, and not the accompanying swelling of the spleen or the lymph-glands, is the specific process, the designation "lienomedullary or medullary lymphatic" must be considered as illogical and confusing.

From a hematologic standpoint, therefore, only two forms of leukemia may be differentiated:

1. Leukemic processes associated with the growth of lymphoid tissue—"*lymphatic leukemia.*"

2. Leukemic processes associated with the growth of myeloid tissue —"*myelogenic leukemia.*"

For the accompanying clinical symptoms one is justified in making simple additions that will not confuse—*e. g.*, "lymphatic leukemia with enlargement of the liver or spleen," "myelogenic leukemia with swelling of the lymph-glands," etc.

From present knowledge, though this is certainly not very definite, one may assume that lymphatic and myelogenic leukemia have a different etiology, especially after Löwit's recent finding of plasmodium-like forms within the white blood-corpuscles in myelogenic which are absent in lymphatic leukemia.

A differentiation of lymphatic from myelogenic leukemia is further evident from the fundamental difference in their general clinical pictures.

Lymphatic leukemia is divided clinically into two forms that are differentiated readily from one another. First, acute lymphatic leukemia, which is characterized by its rapid course, by the small size of the splenic tumor, an inclination to petechiæ and to a general hemorrhagic

[1] As a characteristic example, may be mentioned a case observed by Ehrlich a short time ago. A woman was injured in the region of the spleen by a fall from a scuttle-hole in a roof, and the injury was followed by a gradual but considerable enlargement of the spleen. Since no other clinical symptoms were evident, the surgeon treating her diagnosed pure lienal leukemia, and proposed splenectomy. Examination of the blood, however, showed the appearance of myelogenic leukemia, and the operation was not undertaken.

diathesis. Its foudroyante course invariably produces the impression of an acute infectious disease.

The second form of lymphatic leukemia is differentiated from the preceding by its chronic, frequently very protracted course. The spleen usually shows its participation by a considerable enlargement. Still the investigations are as yet too few to determine whether chronic lymphatic leukemia represents a single disease or must be separated etiologically into subclasses. Hematologically every lymphatic leukemia is characterized by a marked predominance of the lymph-cells, especially of the larger forms. The writer wishes to insist expressly that the number of enlarged lymph-cells is by no means characteristic of acute lymphatic leukemia, since chronic, even very protracted cases show the same. For instance, in such a case in Gerhardt's clinic all the investigators (Grawitz, v. Noorden, Ehrlich) observed these large cells throughout the entire course. Corresponding to previous conclusions (see p. 84), the writer considers that the increase of lymph-cells in the blood in lymphatic leukemia is the result of a passive floating in of these elements, and not an active emigration following chemic irritation.

Myelogenic leukemia presents a totally different picture. In earlier times a differentiation of myelogenic leukemia from simple leukocytosis was very difficult—in fact, both conditions were regarded as only a difference in degree of the same pathologic process, and it was assumed that when the proportion of the whites to the reds exceeded a definite limit (1 : 50) leukocytosis ceased and leukemia began. The fundamental difference of the two conditions was discovered only by the aid of staining methods. Leukocytosis is now recognized as an increase of the normal polynuclear neutrophile leukocytes, while myelogenic leukemia introduces elements into the blood not found there normally. These new forms are so characteristic that the diagnosis of leukemia is possible even in the rare cases in which the entire number of white blood-corpuscles is not greatly increased. The most striking instance of this sort known to the writer is a case of pronounced myelogenic leukemia observed by v. Noorden, in which the proportion of whites to reds was only 1 : 200.

Though misunderstandings and confusion are encountered in the literature in regard to the blood picture of myelogenic leukemia so sharply described by Ehrlich, the responsibility for them must be laid to errors on the part of the observers. It has, for instance, happened that inexperienced observers described cases of lymphatic leukemia as myelogenic. The apparent deviations found under these circumstances have been quoted from one book to another as remarkable cases.

Again, the characteristic elements necessary to a diagnosis—*e. g.*, the neutrophile myelocytes—have often remained unrecognized on account of defective staining technic. Another fertile source of misunderstanding lies in the fact that the typical leukemic picture may be altered under the influence of complicating diseases; for instance, the specific character of the blood-picture may be more or less obliterated by the occurrence of an ordinary leukocytosis the result of a secondary infection. These conditions should naturally be considered separately, and ought not to be allowed to subvert the general disease-picture. Nobody would deny the diagnostic importance of glycosuria in diabetes because in conditions of inanition the sugar may completely disappear, although the diabetes continues, or undervalue the symptom of enlargement of the spleen in typhoid fever because it occasionally disappears as a result of an intestinal hemorrhage.

From these considerations it is evident that the description of leukemic blood should be made from uncomplicated cases and by the aid of established methods. Under these circumstances such a characteristic picture is obtained that the diagnosis of leukemia can be made with absolute certainty from the blood preparation alone. It is necessary to insist on this fact observed hundreds of times, since several recent writers on hematology refuse to recognize its full significance. For instance, v. Limbeck, in the latest edition of his clinical pathology of the blood, says: "An unqualified diagnosis of lienomedullary leukemia can not be made from the blood alone—that is, from the presence of one or several cells. It is necessary to consider not only the general picture of the case, but also the general picture of the blood-finding." Against this the writer asserts that an intelligent hematologist has never diagnosticated a leukemia "from one or several cells." At least, in the work of Ehrlich and his pupils, the character of a leukemia is determined only by the occurrence of a great number of individual symptoms, each one of which is indispensable for the diagnosis, and which become convincing only when taken together. Under these conditions the microscopic examination of the stained blood, apart from any other diagnostic aid, suffices to determine whether leukemia is present, and whether this is of the lymphatic or myelogenic variety.

Myelogenic leukemia, omitting an almost invariable marked increase of white blood-corpuscles, is characterized *microscopically* by a variegated and varying picture. This is produced by the intercurrence of different factors, namely:

A. That in addition to the polynuclear cells, their antecedents, the mononuclear granular leukocytes, are found in the blood.

B. That the participation of all three types of granulated cells, the neutrophiles, eosinophiles, and mast-cells, contributes to the increase of the white blood-corpuscles.

C. That atypical cell-forms—*e. g.*, dwarf forms of different kinds of white blood-corpuscles, and mitotic figures—are discovered.

D. That the blood contains invariably nucleated red blood-corpuscles, often in large numbers.

1. We may begin with a discussion of the *mononuclear neutrophile cells*, Ehrlich's "myelocytes." These are present in such large numbers in the blood of medullary leukemia that they give a mononuclear character to the whole picture. As has been stated, myelocytes normally occur in the bone-marrow, but not in the circulating blood. Their immense importance in the diagnosis of medullary leukemia, in which they have been regularly found by the best investigators, is in no way lessened by their transitory occurrence in several other conditions (see pp. 68 and 69). Though, according to Türk's investigations, they are occasionally found at the crisis of a pneumonia, as an accompanying condition in the general leukocytosis, the danger of a confusion with leukemia does not in the least arise. This is prevented by: (1) the much smaller increase in white cells generally; (2) the diminution of eosinophiles and mast-cells; (3) the fact that the myelocytes of leukemic blood are almost always considerably larger; (4) the predominant polynuclear character of the leukocytosis, which is not concealed by the small number of myelocytes (at most 12 per cent.); and (5) the incomparably smaller absolute number of myelocytes. In a pronounced case of Türk's, for instance, in which the percentage of myelocytes was 11.9, their absolute number amounted at most to 1000 per c.mm. This number can not be compared with that occurring in leukemia, in which 50,000 to 100,000 myelocytes or more per c.mm. are found in by no means extreme cases.

2. *The Mononuclear Eosinophile Cells.*—Even before the introduction of staining, Mosler had pointed out large coarsely granular cells, "Markzellen," as characteristic of myelogenic leukemia. These are in great part identical with the mononuclear eosinophile cells to which Müller and Rieder devoted special attention, and which they considered the eosinophile analogues of the preceding group. They are large, coarse elements with an oval relatively feebly staining nucleus. Though they are undeniably a valuable characteristic of leukemia, their significance is much less than that of the mononuclear neutrophile cells on account of the numbers of the latter. The presence of "eosinophile myelo-

cytes" is not an absolute proof of leukemia, since they sometimes occur in small numbers in other diseases.

3. *The Absolute Increase of Eosinophile Cells.*—It was stated by Ehrlich in his first work on leukemia that the absolute number of eosinophiles was invariably increased in myelogenic leukemia. This statement did not remain uncontradicted, and v. Limbeck, in his text-book, speaks of an "alleged" increase of eosinophile cells. It was the well-known work of Müller and Rieder that gave rise to this opposition and aroused suspicion as to the diagnostic importance of eosinophile cells. Still, these writers based their contradiction on false premises.

Ehrlich did not affirm an increase in the percentage of eosinophiles, but only in their absolute numbers. When a normal percentage of eosinophiles is found in a case of leukemia, this invariably indicates a considerable absolute increase, and Müller and Rieder would have found Ehrlich's assertion confirmed if they had reckoned the absolute numbers in several of their cases. Selecting from the seven cases studied in their work those in which it is possible from the given data to show the absolute number of eosinophile cells, it is found that:

Case 29	3.5 per cent. eosinophiles	14,000 per c.mm.
" 30	3.9 " "	8,000 " "
" 31	3.4 " "	11,000 " "

In contrast to the number of eosinophiles stated by Zappert to be a high normal, namely, 250 eosinophiles, in these cases an average of 11,000, or almost fifty times that number, is found. The findings of Müller and Rieder, therefore, fully confirmed Ehrlich's assertion.

The absolute number of eosinophile cells depends to a certain extent on the relative proportion of whites and reds, and is increased in proportion to the general increase in leukocytes. Zappert found—*e. g.*—in his cases the following figures:

Relation of white to red blood-corpuscles.	Absolute number of eosinophiles.
1:24	3,000–4,560
1:18	3,300
1:15	7,000
1:13	8,700
1:11	6,000
1:7.6	8,300
1:7.0	7,600
1:7.0	29,000
1:5.0	14,000
1:3.8	34,000

Apart from the general correspondence of the two series of figures, this summary shows the minimum, 3000 eosinophiles, with a proportion of whites to reds of 1 : 24, still fifteen times above the normal. The maximum number of 30,000 found by Zappert is by no means an

extreme, for cases of leukemia are not at all rare in which 100,000 and more eosinophiles per c.mm. are found.

After a glance at these figures it must be admitted that the absolute increase of eosinophile cells in medullary leukemia is not "alleged" (v. Limbeck), but, on the contrary, decidedly real and considerable.

Though as a result of complications, like sepsis, the absolute and relative number of eosinophile cells in leukemia may decrease, this can not be considered a deviation from the rule that the eosinophile cells are increased in myelogenic leukemia. For even here it is only necessary to observe the obvious principle of comparing analogous conditions with one another. The blood of a leukemic patient affected with severe sepsis should not be compared with that of health, but with that of a person likewise affected with severe sepsis. In sepsis it is known that the number of eosinophiles decidedly decreases, so that, for instance, Zappert in five such cases was unable to find any eosinophiles in the blood. In contrast to this there is a case of myelogenic leukemia described by Müller and Rieder which was complicated by a severe suppurative process that terminated fatally. As a result of the acute neutrophile leukocytosis produced by the septic infection, the number of eosinophiles sank rapidly from 3.5 to 0.43 per cent. (four hours ante mortem). Still the absolute number of eosinophile cells at this terminal stage amounted to 1400–1500 per c.mm., which in comparison with a simple sepsis is a great excess. It is, therefore, unjustifiable from such cases to contest the diagnostic significance of eosinophile cells in leukemia, since they actually show a striking confirmation of the constancy of the rule.

At the time when Ehrlich stated the principle of the diagnostic significance of eosinophiles in leukemia, simple eosinophile leukocytosis (see p. 112) was not known, and was discovered only later in asthma and other conditions. Yet this does not subvert the applicability of this rule, since a confusion of the other conditions producing eosinophilia with leukemia is absolutely excluded, as they show no other clinical resemblances and the blood-picture differs in several important particulars: (1) the total increase of white cells rarely reaches numbers which recall leukemia; (2) the (non-leukemic) eosinophile leukocytoses are exclusively polynuclear; (3) mast-cells and neutrophile myelocytes are almost entirely wanting.

The diagnostic significance of an absolute increase of eosinophile cells is further shown by cases in which, with a blood-picture recalling leukemia, the absence of eosinophile cells excluded such a diagnosis. Thus, for instance, in a case of carcinoma of the bone-marrow described

by Epstein, there was found a condition of anemia, which is almost always present in leukemia, together with a very marked increase of white blood-corpuscles, numerous neutrophile myelocytes, and nucleated red blood-corpuscles. Everyone who, like Müller and Rieder, considers the number of eosinophiles not essential to the diagnosis, must have diagnosticated a myelogenic leukemia, yet, following Ehrlich's rule, this would have been absolutely excluded by the absence of eosinophiles.

It appears, therefore, that an absolute increase of eosinophile cells must be regarded as indispensable in the diagnosis of leukemia.

4. *The Absolute Increase of Mast-cells.*—Mast-cells are invariably increased in myelogenic leukemia. They may be recognized and counted either by the triacid or the eosin-mythelene-blue stain. Under the action of the first they appear as polynuclear non-granular cells, since their granulations do not take up any of the triacid constituents, and in Uthemann's dissertation they were thus described. It was only later that Ehrlich recognized them as mast-cells, and he was confirmed among others by C. S. Engel.

The increase of mast-cells in all cases of myelogenic leukemia is absolute and considerable. Ordinarily they are half or possibly quite as numerous as the eosinophiles, but they sometimes exceed them in number. It is consequently obvious that the mast-cells undergo a comparatively greater increase than the eosinophiles, since they normally amount to about 0.28 per cent. Their diagnostic importance in myelogenic leukemia is probably greater than that of the eosinophile cells for the reason that up to the present no other condition is known in which there is a marked increase of the mast-cells.

5. *Atypical forms of white blood-corpuscles:* (*a*) Dwarf forms of polynuclear neutrophiles and eosinophiles were first described by Spilling in leukemia. As a rule they represent normal polynuclear cells in smaller forms. (*b*) Dwarf forms of mononuclear neutrophiles and eosinophiles are also found, and correspond to the pseudolymphocytes described in another place (see p. 69). The significance of dwarf forms in leukemia is not clear, and it is difficult to decide whether they enter the circulation as such or decrease in size in the circulation by division and contraction. (*c*) Cells showing mitoses. Formerly considerable significance was attached to mitoses in leukemic blood, under the supposition that they indicated an increase of white blood-cells by a process of division in the circulation. This assumption was especially advocated by Löwit. A number of authorities (H. F. Müller, Wertheim, Rieder) have demonstrated mitoses, especially of the myelocytes, in the

circulating blood in leukemia. Still no diagnostic value can be attributed to them. In the first place, they become evident only on the employment of special stains; and secondly, they are invariably present in extremely small numbers. Müller, for instance, declared that he was ordinarily obliged to examine thousands of white blood-corpuscles before meeting one in mitosis. He found only one case in which the karyokinetic figures were in larger numbers, and even here there was only one in mitosis among several hundred leukocytes. This practically negative finding teaches that the mitoses play a much too subordinate rôle to indicate that they are of any significance as far as the increase of cells in the blood is concerned.

6. *Nucleated Red Blood-corpuscles.*—These are a constant constituent of leukemic blood. In different cases their numbers vary considerably. In one they are extremely scanty, in another every field contains many of them. The normoblastic type is found most frequently, though megaloblasts and transitions between the two forms are not infrequent. Mitoses of the erythrocytes have been described by different writers, though they possess no theoretic or clinical significance.

The occurrence of erythroblasts in leukemia may be either a specific symptom or only an expression of the anemia accompanying the leukemia. The writer is inclined to decide in favor of the former, since such immense numbers of nucleated red cells are practically never observed in other anemias.

So much for the individual elements of leukemic blood, on which the diagnosis of the disease is based. Still, it must be added that though every individual element is found in every case of medullary leukemia, its manner of occurrence and its numerical ratio to others are extremely variable. Apart from the increase in leukocytes, every case is different; in one case the blood-picture is dominated by mononuclear neutrophiles with large nuclei; in another the increase of eosinophiles is most conspicuous; in a third the nucleated red blood-corpuscles predominate; in a fourth the blood is filled with mast-cells. Therefore, such an abundance of combinations is found that every single case possesses an individual stamp.[1]

The study of the alterations of the blood in medullary leukemia under the influence of certain intercurrent affections is decidedly important. From the recent investigations of A. Fränkel, Lichtheim, and others,[2] it appears that under the influence of febrile diseases the

[1] Ehrlich once succeeded in recognizing, by estimations of the different cell-forms, the specimens belonging to ten different cases of leukemia, the labels of which were lost.

[2] For the literature on the subject, see A. Fränkel.

number of leukocytes may experience an extraordinary decrease. The character of the blood alters in such a way that the myelemic elements become less conspicuous, while the polynuclear neutrophiles come more to the front. These may reach percentages such as are seen in ordinary leukocytoses, of 90 per cent. and over. Further details in regard to these remarkable cases, their theoretic significance, and their clinical course, have been reserved for the special part on Leukemia.

Here only certain rare cases will be alluded to which demand attention on account of such a transformation of the leukemic blood that the diagnosis was made exceedingly difficult or almost impossible. In the literature only one such case is found. Zappert reports the case of a female patient who, in February, 1892, presented the typical picture of myelogenic leukemia; among other symptoms the proportion of whites to reds was 1 : 4.92, with 1400 eosinophiles per c.mm., or 3.4 per cent. At the end of September, in the same year, when the patient was brought into the hospital, where she quickly died of progressive inanition, the count showed a proportion of whites to reds of 1 : 1.5, an eosinophile percentage of 0.43, and about 70 per cent. of mononuclear leukocytes, the majority of which were free from neutrophile granulations. Moreover, Zappert expressly insists that the whole appearance of these cells differed from that of lymphocytes. At the autopsy Zappert found in the bone-marrow large numbers of non-granular mononuclear cells and a much smaller number of eosinophile cells than is usual in leukemia. A second case of this kind was examined by Dr. Blachstein, under Ehrlich's direction. The patient in question had been subjected to an accurate clinical examination some time before on account of myelogenic leukemia. After admission to the hospital the blood examination was made only one day before the exitus lethalis, which was the immediate result of a septic complication. The blood showed a markedly leukemic character with 62 per cent. polynuclear cells, 17.5 per cent. mononuclear non-granular myelocytes of about ordinary size, 0.75 per cent. eosinophile cells, and moderate numbers of nucleated red blood-corpuscles. The predominance of polynuclear cells and the small number of eosinophiles are readily explained by the septic infection, though the absence of granules in the mononuclear cells is striking.

These two observations can be explained only by the assumption that in certain terminal stages the organism loses its power of elaborating neutrophile substances. Analogous conditions are also found in non-leukemic diseases, for instance, the case of post-hemorrhagic anemia described by Ehrlich. It is very important to recall these rare cases,

thus far but little studied, since ignorance of them may give rise to errors as to the origin of the mononuclear cells and to the diagnosis of lienal leukemia.

In conclusion, the writers wish to take up the important question of **the origin of the myelemic constituents of the blood.** According to their explanation, two possibilities must be considered, either a passive inundation or an active emigration of the bone-marrow elements into the circulation. This important and difficult question is by no means ready for decision. The most serious objection raised against the active emigration of the bone-marrow cells is deduced from the behavior of the white blood-corpuscles on a warm stage. Such investigations were undertaken by a number of men, of whom must be mentioned Biesiadecki, Neumann, Hayem, Löwit, Mayet, Gilbert, and especially H. F. Müller. All these investigators agree that the lymphocytes under no circumstances show the slightest motility, while the polynuclear neutrophiles are invariably motile. [A number of recent investigators have come to the conclusion that the lymphocytes are actively ameboid, and the contention seems to be conclusively established by the studies of Maximow,[1] Almkvist,[2] Hirschfeld,[3] Mosse,[4] Flexner,[5] Bunting,[6] and Wolff.[7]

In this connection the view of Prof. Welch is of interest. He has always held that evidence in support of the movement of the lymphocytes was conclusive, and was led to that belief especially by the observations of Gilchrist in urticaria. He found that they accumulate within fifteen minutes of the application of an irritant, evidence that there must be active migration of the lymphocytes.—ED.].

As far as the elements most characteristic of leukemia, namely, the myelocytes, are concerned, the literature is contradictory. Some authorities deny all motility to these cells, though the majority report slight movement which renders the negative results valueless. In a

[1] "Experimentelle Untersuchungen über die entzündliche Neubildung," *Ziegler's Beiträge*, 5tes Supplementheft, 1902.

[2] "Ueber die Emigrations-fähigkeit der Lymphocyten," *Virchow's Archiv*, 1902, vol. clxix., p. 17.

[3] "Sind die Lymphocyten amäboider Bewegung fähig," *Berlin. klin. Wochenschr.*, 1901, vol. xxxviii., p. 1019.

[4] "Zur Histogenese der lymphatischen Leukemie," *Zeitschr. für klin. Med.*, 1903, vol. l., p. 70.

[5] "The Pathology of Lymphotoxic and Myelotoxic Intoxication," *Univ. of Penna. Med. Bull.*, 1902, vol. xv., p. 237.

[6] "The Effects of Lymphotoxin and Myelotoxin on the Leukocytes of the Blood and on the Blood-forming Organs," *Ibid.*, 1903, vol. xvi., p. 200.

[7] *Arch. de Méd. expérim.*, 1902, xiv., 6, p. 754.

recently published careful work from the Collège de France, Jolly makes a similar statement, namely: "C'étaient des changements de forme sur place, lents et peu considérables, formations de bosselures à grands rayons, passage d'une forme arrondie à une forme ovalaire ou bilobée, etc. Ces mouvements étaient visibles dans les observations I et IV et appartenaient surtout à des globules de grande taille." It is naturally impossible to decide if this slight motility is sufficient to indicate independent locomotion, though a further observation of Jolly's relative to the mononuclear eosinophile myelocytes seems to support it. So far it has been generally believed that the latter possess no independent motility, yet in a recent case of typical leukemia Jolly found almost all the eosinophile cells on the preparation in active movement. He says: "Ces globules granuleux acrifs présentaient des mouvements de progression et des changements de forme caractéristiques et rapides; cependant je n'ai pas vu ces globules présenter de pseudopodes effilés; de plus, leurs contours restaient presque toujours assez nettement arrêtés. Ces particularités correspondent exactement à la description, qu'a donnée depuis longtemps Max Schultze des mouvements des cellules granuleuses du sang normal." The examination of the stained specimen from this same case showed that the blood contained, as was to be expected, both polynuclear and mononuclear eosinophile cells. Contrary, therefore, to all previous observers, Jolly perceived a lively active motility of the mononuclear eosinophile cells. That this ameboid movement of the mononuclear cells is rarely seen, is due not to lack of function *per se*, but to defective methods of examination, which are obviously rough and ill adapted to this delicate biologic process. What effects these methods can produce on cells of incontestable motility, is shown by numerous examples in the literature. Rieder, for instance, in a case of malignant lymphoma failed to find any motility in the majority of the polynuclear neutrophiles, though according to all experience this is a property which they invariably possess.

The conclusion, therefore, seems evident that the motility of the mononuclear cells, both eosinophile and neutrophile, seems slight on account of the rough methods of examination; as a matter of fact, the movement is undoubtedly sufficient for emigration.

Another, but much less important objection to the consideration of myelogenic leukemia as an active leukocytosis, is that the pus produced artificially in leukemic patients almost always consists of the same histologic elements as ordinary pus. Still, from what has been said, only a myelemic pus could be expected when the specific virus of

leukemia was present in a concentrated form at the site of inflammation. In Neusser's pemphigus case an eosinophile suppuration was seen only in the idiopathic pemphigus vesicles, not in the artificially produced foci of suppuration. Moreover, it is known that the myelocytes are not at all positively influenced by the chemotactic irritation of ordinary infectious agents; on the contrary, judging from the previous observations on the transformation of the leukemic blood-picture under the influence of infectious diseases, the ordinary bacterial toxins have negatively chemotactic action on the eosinophile as well as the neutrophile mononuclear cells. Under these circumstances it is only natural to expect that an artificially produced suppuration in a leukemic patient would not show a myelemic, but a polynuclear neutrophile character.

It is a problem for future investigation to examine accurately spontaneous inflammatory products—*e. g.*, pleuritic exudates—in order to find out if under particular conditions all the leukocytes characteristic for leukemia may not be able to emigrate from the blood. In one case of pleurisy in a leukemic patient Ehrlich was led to think from a study of the preparation that a "myeloid" emigration, involving all the elements present in the blood, had actually taken place. This observation is not absolutely convincing, inasmuch as it was impossible to estimate exactly the ratio of the red to the white blood-corpuscles in the exudate. Such an estimation would naturally be necessary to determine whether the white blood-corpuscles actively emigrated into the exudate or left the vessels purely mechanically, *per rhexin.*

The assumption of an active origin of myelemia is supported by further considerations. In addition to the myelocytes, the polynuclear leukocytes, the active emigration of which is beyond doubt, are enormously increased in leukemia. Now if it is concluded that the mononuclear cells are passively forced into the circulation, we must resign the simple theory of uniform origin of the different elements and fall back on a very elaborate explanation.

Moreover, the morphologic alterations of leukemic blood under the influence of infectious diseases can be logically explained only by the theory of emigration. For if the white blood-corpuscles were mechanically forced from the bone-marrow, it would be impossible to understand how a bacterial infection would be able to change the condition to a polynuclear leukocytosis; while this is readily explained by the assumption that the ordinary bacterial toxins act positively chemotactic only on the polynuclear neutrophiles and negatively chemotactic on the other forms.

In regard to the origin of the leukemic blood-picture, therefore, it must be concluded that under the influence of the specific leukemic virus not only the mature polynuclear elements, but likewise their mononuclear eosinophile as well as neutrophile antecedents wander into the blood; in other words, myelogenic leukemia is to be reckoned with great probability among the active leukocytoses.

DIMINUTION OF THE WHITE BLOOD-CORPUSCLES (LEUKOPENIA).

Diminution of the white blood-corpuscles plays a very unimportant clinical rôle in comparison with their increase. It occurs in only a few diseases, and rarely reaches a high grade. The greatest decrease was described by Koblank in the following case, while making systematic examinations in Furbringer's ward: A twenty-five year old robust man whose internal organs were found healthy, suffered from short epileptiform attacks, in one of which death occurred. The postmortem examination showed no cause for death. In the course of three days' observation two blood examinations were made, of which the first showed in ten cover-glass preparations not one white blood-corpuscle, the second in the same number of preparations a single example.

This remarkable case has been mentioned on account of the extreme leukopenia, such as was never before observed. An explanation of it is impossible on account of the vagueness of the whole case.

In general the conditions are very well known under which considerable diminution of the leukocytes takes place. These may be divided into two chief groups:

1. Leukopenia due to destruction of a portion of the white blood-corpuscles (Löwit).

2. Leukopenia due to a lessened influx of white blood-corpuscles.

(*a*) In infectious diseases on account of negative chemotaxis;

(*b*) In anemias, etc., on account of defective function of the bone-marrow. [In this place, the constant leukopenia of certain cases of so-called splenic anemia should be recalled. In several instances of this sort under the writer's observation, the number of leukocytes has remained very low without exception during many months, and even such infectious diseases as pneumonia and cellulitis, that ordinarily provoke a decided leukocytosis, caused no increase, or, at least, not any increase above the lower normal number of white cells. In these cases there was no special degree of anemia.—Ed.]

In the chapter on Leukocytosis the leukopenia experimentally produced by Löwit was thoroughly explained and it was shown that according to present views this was the result not of an actual destruc-

tion of white elements, but of an altered distribution within the circulation.

Among the infectious diseases associated with a hypoleukocytosis must be mentioned, in the first place, typhoid fever. In this the diminution is mostly at the expense of the polynuclear cells. Uncomplicated measles also usually runs its course with a pronounced leukopenia which is especially conspicuous during the eruption and at the height of the exanthem. These cases of infectious leukopenia are explained not so much by a destruction of white blood-corpuscles, as by a decreased influx, which in the case of the polynuclear elements is to be referred to the presence of negatively chemotactic substances in the circulation.

In certain cases of severe anemia leukopenia has a special significance in that it makes the prognosis unfavorable. Ehrlich described [1] a case of post-hemorrhagic anemia ending fatally in which a marked diminution of the leukocytes was found. The count showed that the greatest number (80 per cent.) of the white blood-corpuscles were lymphocytes, while the polynuclear cells amounted only to 14 per cent. (instead of the normal proportion, 70–72 per cent.). No eosinophiles or nucleated red blood-corpuscles were observed. Ehrlich attributed this to a disturbance of the function of the bone-marrow, which resulted in an insufficient production of red and white blood-corpuscles. As an anatomic basis for this disturbance of function, he conjectured that the fat-marrow of the long tubular bones was not transformed into blood-making red marrow, as is usually the case in severe anemias. This diagnosis made *intra vitam* in two cases was fully confirmed by autopsy.

Blood-platelets—Blood-dust.—The **blood-platelets** were first described by Hayem, later by Bizzozero, as a third formed element of normal blood. They are round or oval, hemoglobin-free discs. Their shape is extremely susceptible to mechanical, thermic, and chemic influences. Their size is about 3 μ. They are especially characterized by an extraordinary adhesiveness which inclines them to form masses or "clusters." This makes it very difficult to separate the blood-platelets from the other formed elements, and renders accurate counting of them almost impossible. The employment of the ordinary apparatus used in the counting of blood-corpuscles is decidedly unsatisfactory, since the platelets adhere to its walls. Previous investigators—*e. g.*, Bizzozero—endeavored to counteract this obstacle by employing a special diluting fluid which would prevent the running together of the platelets, but this did not prevent them adhering to the wall of the capillary tube of the mixing apparatus in considerable numbers.

[1] *Charité-Annalen*, 1888.

Brodie and Russell recently proposed a new mixture in which the platelets remain isolated and are at the same time stained. The blood drop is allowed to issue from the wound into a drop of the solution, and they estimate the number of platelets from their relation to the red blood-corpuscles.[1]

Their solution consists of: dahlia-glycerin, 2 per cent. salt solution, equal parts.

Another method advocated by the majority of recent investigators is their relative estimation in stained preparations. In preparations treated by the iodin-eosin method (see p. 46) Ehrlich found that, corresponding to their high alkalinity, the blood-platelets become conspicuous by their intense red stain and are consequently readily estimated. Much less practical and by no means more accurate is Rabl's new method, based on the stain with iron hematoxlin, proposed by M. Heidenhain for the demonstration of centrosomes. A procedure advocated by Dr. Rosin, but not yet published, is more practical. This consists in fixing the dry preparation for twenty minutes in osmic acid fumes, and staining it in a concentrated watery methylene-blue solution.

As to the *significance* of the blood-platelets, the majority of authorities, among whom Hayem, Bizzozero, and Laker, may be especially mentioned, assumed that they are preformed in the living blood. The opposite view, advocated particularly by Löwit, that they arise only after the blood has been removed from the vessels, is not supported by the writer's observations.

On account of their small size and the entire absence of nuclear substances the blood-platelets are not generally regarded as actual cells. Yet whether they represent intravital separations of plasma bodies or are excreted from the cells, has not been determined, even though many circumstances appear to support the latter assumption. The fact that they contain glycogen (see p. 45) seems especially to characterize them as derivatives of the blood-cells. Moreover, in stained preparations forms are frequently seen which would arouse the suspicion that the blood-platelets came from the red blood-corpuscles (Köppe). Finally Arnold observed in the mesentery of young guinea-pigs not only extravascularly but also intravascularly a cleavage of the red blood-corpuscles, with transformation of the separated elements into hemoglobin-free forms.

[1] The physiologic numbers found by Brodie and Russell by this method exceed considerably those of previous investigators. They found a ratio of platelets to erythrocytes of 1:85 or an absolute number of about 635,000 per c.mm.

[Deetjen[1] has published an important article in which he claims the independent nature of the plaques. His method of examining the fresh blood is an important part of his article. A solution of agar is prepared by dissolving 5 grams of agar in 500 c.c. of distilled water and boiling for half an hour. The liquid is filtered hot, and to each 100 c.c. of it are added 0.6 gram of common salt (NaCl) and 6 to 8 c.c. of a 10 per cent. solution of $NaPO_3$. The last solution must be prepared without heat. Then 5 c.c. of a 10 per cent. solution of K_2HPO_4 are added. A small amount of this agar is put on a glass slide and allowed to cool. A small central depression is scooped out and a drop of blood is placed in this, covered with a cover-glass, and examined at 40° C. In such a cell the movements of the corpuscles are retained for a considerable time. The specimen may be fixed by allowing Flemming's solution or osmic acid to run under the cover-glass. He found that in such preparations the blood-plaques are round or oval discs, but also showed ameboid movements. At the height of the movements an inner, highly refractive, greenish portion, and an outer, clearer portion, from which pseudopods are projected, can be distinguished. Deetjen concludes that the blood-plaques are distinct formations with nucleus and ameboid movements.

By various staining methods he was able to differentiate what he considered the nucleus from the surrounding protoplasm, though he thought it difficult to determine whether this is a true nucleus or a massing of chromatin. He describes certain changes which he regarded as degenerative and necrotic alterations.

A number of authors, including Engle, Maximow, and Pappenheim, have concluded from their investigations that the plaques are derivatives of the red corpuscles, being, in fact, extruded "inner-bodies" or remnants of the nucleus. Arnold regards them as simple fragmented portions or separated buds of red cells, a conclusion which agrees with the author's own observations. On the other hand, De Khuyzen,[2] using a different method, agrees substantially with Deetjen, as do also Kopsch,[3] Argutinsky,[4] Morawitz,[5] and Dorendorf and Hamel.[6]

Wlassow and Sepp,[7] however, oppose the conclusions of Deetjen regarding the blood-plaques. They deny that these structures contain a nucleus, and refer the appearances recorded by Deetjen to the action of

[1] *Virchow's Archiv*, Bd. clxiv., p. 239. [2] *Anatom. Anzeiger*, 1901, Bd. xviii.
[3] *Ibid.* [4] *Ibid.* [5] *Deutsch. Archiv. f. klin. Med.*, 1904, Bd. lxxix.
[6] *Münch. med. Wochenschr.*, Nov. 12, 1901.
[7] *Centralbl. f. allg. Pathol. u. pathol. Anat.*, 1902, xiii., 12, p. 465.

the medium in which he preserved the corpuscles and made his observations.

In a review of Deetjen's article[1] the editor expressed the view that the phenomena observed by Deetjen might be entirely due to physical conditions, and cited his own experience with degenerative changes in red corpuscles and amebae. Not rarely small spherical bodies can be broken off from the parent red corpuscle or from an ameba by the effects of heat or chemic agents. These small extruded bodies present the features seen by Deetjen. The writer's own view has been for a long time that the red corpuscles are the source of the blood-plaques.

Hirschfeld[2] came to a similar conclusion as a result of studies made with dried preparations of blood.

Schwalbe[3] believes that the blood-plaques originate from the leukocytes as well as from the erythrocytes.—Ed.]

Our knowledge of the physiologic function of the blood-platelets is likewise very incomplete. The original view of Hayem, that they were early stages of the red blood-corpuscles, on account of which he designated them "hematoblasts," is, according to the majority of hematologists, without foundation.

Almost all recent works (compare Löwit's view) recognize a close relation between blood-platelets and clotting. This was first noticed by Bizzozero. Whether the material for the formation of fibrin comes directly from the platelets, as Bizzozero contends, or whether the platelets, corresponding to the observations of Eberth and Schimmelbusch on thrombosis, play only an intermediate rôle, has not been determined. To go into the chemistry of this complicated problem would lead us too far, and the writer will content himself, therefore, with presenting a few clinical observations to illustrate the relation between the coagulability of the blood and the number of platelets.

Marked increase of the blood-platelets is found especially in chlorosis (Muir) and post-hemorrhagic anemia (Hayem). In both conditions the increased coagulability of the blood is pronounced. In contrast to this there is the important observation of Denys, who found in two cases of purpura in which the coagulability of the blood was markedly decreased, or even absent, a striking diminution of the platelets as the only morphologic alteration of the blood. Ehrlich also had the opportunity of examining a similar case in which the blood-platelets were entirely absent.

Blood-dust.—A fourth formed constituent of the blood was described

[1] *Progressive Medicine*, June, 1902. [2] *Virchow's Archiv*, Bd. clxvi., Heft 2.
[3] *Wien. klin. Rundschau*, 1903, xvii., 9, p. 157.

by H. F. Müller and designated "blood-dust." These particles are found in the plasma of the blood, and are very small granules or cocci-like, colorless, strongly refractive bodies of lively molecular movement, which persist for a long time without any special precautions in the examination. According to Müller, they do not stain with osmic acid, and, therefore, probably contain no fat. They appear to have no connection with fibrin-formation, since they always occur outside the fibrin net. Müller found them in every normal blood, though in varying numbers. They were markedly increased, among other conditions, in a case of Addison's disease, and decreased in starvation and in cachexias.

[Stokes and Wegeforth [1] and Nicholls [2] concluded from investigation that these bodies are extruded granules of leukocytes, as did also Horder.[3] Türk has recently [4] expressed the same view. Others have conjectured that they represent degeneration-products of either the white or red corpuscles.—Ed.].

Douglas and Hardy [5] have studied the character of the white corpuscles in the blood, and refer to 50 cases of bilharzia, finding that (1) the percentage of coarse-grained eosinophile leukocytes is nearly always much above the average found in the normal blood; (2) that this increase is proportioned to the diminution of the polymorphonuclear cells; (3) that there is less frequently an increase in the mononuclear leukocytes corresponding in such cases to a diminution of lymphocytes. The leukocytes of the urine are coarse-grained eosinophiles in a very large proportion, the remainder being almost all polymorphonuclear and lymphocytes, and large mononuclear cells being very uncommon.

Further investigations are necessary to determine their chemic nature, especially extraction experiments with ether, the employment of fat-staining substances, as alkanna and sudan, and comparative examinations of lipemic blood.

[1] *Johns Hopkins Hosp. Bull.*, Dec., 1897.
[2] *Phila. Med. Jour.*, Feb. 26, 1898.
[3] *Lancet*, Oct. 14, 1899.
[4] *Verlesungen über Hæmatologie*, 1904.
[5] *Lancet*, Oct. 10, 1903.

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[1] On account of the superabundance of hematologic literature, the writers have been forced to limit themselves in this list to the important and recent papers. For this reason publications are repeatedly indicated in which a review of the literature on the topic in question may be found.

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CLINICAL FEATURES OF ANEMIA.

INTRODUCTION.

IN order to obtain a general grasp of anemia we must recur to the definition proposed at the beginning, which designated it as "a quantitative or qualitative diminution in the amount of blood."

In addition to a physiologic capability of alteration which is not slight, the blood possesses an extraordinary power of preserving its normal composition. It compensates not only for the very fine alterations in its composition, not appreciable to our senses, which it is continually experiencing in its ceaseless changing relations to the organs, but is also capable of withstanding to a surprising degree many coarse influences, as, for instance, many experiments. Foreign bodies, the smallest particles of coloring-matter, bacteria, etc., are excreted from the circulation as rapidly as they can be introduced. Even chemic foreign substances or abnormal amounts of normal constituents introduced into the blood are usually so quickly excreted that after a few circulatory cycles no trace of the interference is percetible.

Just as in these experiments, the blood preserves its normal composition under the influence of numerous factors which affect the organism in general or the blood in particular. Severe diseases of vitally important organs may run a regular course without any recognizable alteration in the blood. Moreover, there may be frequently repeated slight losses of blood without even a transitory abnormality becoming evident.

This power of resistance naturally has its limits, both in regard to the kind as well as to the duration and the intensity of the inimical influence, since the continuance of the normal composition depends on constancy of the relation between blood formation and blood destruction. A decrease in the blood formation without a corresponding diminution in blood destruction must produce a disparity, just as an increased destruction without a progressive new formation. Therefore, all conditions which act unfavorably either mediately or immediately on

the destruction or new formation of blood are capable of lessening the amount of blood—*i. e.*, of producing anemia.

The *new formation of blood*—*i. e.*, the physiologic replacement of blood destroyed by functional activity—is still very inadequately understood as to its true nature and its dependence on external influences. Nevertheless we are undoubtedly justified in assuming that a normal formation of blood is possible only (1) when the blood-making organs, especially the bone-marrow, are healthy; (2) when the material necessary for its manufacture is quantitatively and qualitatively sufficient.

One, therefore, finds anomalies of the blood when the hematopoietic system is diseased or when as a result, for instance, of inanition, the material for the formation of new blood is decreased or poor in quality ("hypoplastic form of anemia," Immermann).

Increased destruction of blood is directly produced by hemorrhage, indirectly by an increase in the physiologic consumption of the blood-tissue or by pathologic processes, especially the abnormal excretion of albuminous material—*e. g.*, in suppuration, albuminuria, etc. ("consumptive form of anemia," Immermann).

It is evident that this theoretic division can not be preserved in concrete cases, since blood consumption and blood replacement necessarily influence one another very closely. In the majority of anemic conditions, therefore, we see a combined disturbance of both these functions ("complex anemia," Immermann).

Though this classification is valuable in general pathology, it is not available for the special study of anemic conditions. The great frequency and polyform character of anemias make the problem of classification extremely difficult, especially since, in several very important points, our knowledge is incomplete. Looking through the numerous recent text-books and manuals on anemia, we can scarcely find two which agree in their definition of individual forms. Moreover, it is absolutely impossible to make an etiologic classification on the basis of our present knowledge without separating forms that naturally belong together and combining very different forms under the one head.

The most frequently employed classification is into primary or idiopathic, secondary or symptomatic anemias. This includes chlorosis and progressive pernicious anemia in the first, all other conditions in the second. Still in this classification the important bothriocephalus anemia is omitted because, according to the principle of classification, it should be reckoned among the secondary, while according to its chief characteristics it belongs among the so-called pernicious anemias. It is, moreover, evident that "pernicious anemia" has been given this special

place only because its cause is unknown. Therefore, whether it is eventually referred to blood or intestinal parasites or purely toxic influences, its designation "primary idiopathic" anemia will be untenable (see Part I., p. 44).

We must, therefore, for the present, hesitate, and abandoning a causal classification, separate the different forms of anemia according to the peculiarities which they manifest in relation to the normal anatomy and physiology of the blood. On this principle the following classification is made:

Simple anemia:
- Acute post-hemorrhagic anemia;
- Simple chronic anemia;
- Chlorosis.[1]

Progressive pernicious anemia.

[1] That chlorosis has a special position among the anemias is evident from the fact that a special discussion is devoted to it in this volume by v. Noorden.

SIMPLE ANEMIA.

ACUTE POST-HEMORRHAGIC ANEMIA.

ACUTE post-hemorrhagic anemia makes a very appropriate introduction to a discussion of anemic conditions. In the first place, its manner of origin is the clearest. Secondly, we see in it all the important changes both of the blood and the other organs which appear as the anemic reaction of the organism. Finally, it offers a more favorable opportunity than any other form of anemia of answering the confusing questions by exact experiments on animals and frequently on man—*e. g.*, after venesection.

Among the acute post-hemorrhagic anemias may be reckoned all alterations which are produced by a loss of blood in a relatively short time—that is, from a few minutes to several days.

THE ORIGIN OF ACUTE POST-HEMORRHAGIC ANEMIA.

An entirely uncomplicated form of acute anemia occurs when a healthy individual suffers an external loss of blood by trauma. Certain differences in the primary symptoms, in the course, in the diagnosis, and therapy, are evident when the hemorrhage occurs internally into a body cavity, especially if the individual was in an abnormal or pathologic condition before the hemorrhage. Still, these differences are too slight to require a subclassification, and it will be sufficient here and there to draw attention to them.

Wounds of large vessels accompanied by a severe loss of blood may occur in accidents of every kind as well as in operations. Since they are so difficult to recognize it is worth while to mention those wounds that are unassociated with injury of the integument—such, for example, as the tearing asunder of large trunks in the extremities, the rupture and tearing of vessels in the large abdominal organs, especially the liver, spleen, and kidneys.

The abnormal—that is, pathologic—conditions of the organism in which severe spontaneous hemorrhages frequently occur are: 1, abortion and the puerperium; 2, tubular pregnancy with rupture of the tube; 3, tumors of the uterus; 4, ulcus ventriculi, duodeni; 5, typhoid fever; 6, carcinoma ventriculi, intestini, hepatis; 7, hemoptysis from

tuberculosis pulmonum; 8, hemoptysis from diseases of the circulatory apparatus, especially aneurysms; 9, varicose veins of the lower extremities, more rarely of other places—*e. g.*, esophagus, hemorrhoids; 10, epistaxis; 11, hemorrhagic pancreatitis; 12, all constitutional anomalies belonging to the group of hemorrhagic diatheses.[1]

The size of the hemorrhage and the severity of the consequent symptoms depend on the cause of the hemorrhage.

Small hemorrhages from, for instance, epistaxis, normal menstruation, small wounds, produce no clinically evident alteration in the composition of the blood. At the same time, however, psychic influences may cause marked abnormalities in the distribution of the blood in the shape of a local anemia of the skin or of the brain, manifested by intense pallor or vertigo, and these may occasion confusion with true general anemia. The short duration, however, prevents errors in diagnosis.

Moreover, it is known from venesection experiments that the loss of even a small quantity (50 to 70 c.c.) causes a deterioration in quality (see below) of the healthy blood; in other words, in a strict sense produces an anemia. Naturally the larger the hemorrhage the greater and more varied are the pathologic changes. The rapidity of the hemorrhage is likewise of no little influence, for it is very evident that considerable difference would be manifest, depending on whether the same amount of blood was lost within several minutes or several days.

Large peracute hemorrhages are accompanied by a series of general and localized disturbances which may be briefly described as follows:

The symptom invariably appearing first is a marked pallor of the skin, the lips, and the conjunctivæ, which frequently reaches a very high grade. Corresponding to the pallor, the body, especially the extremities, feels cool. In persons who are not robust, this first stage is also accompanied by psyhcic disturbances (see below) in the shape of vertigo, fainting, and marked subjective weakness. A symptom that may appear immediately after the pallor, even in persons who are not alarmed or those who have failed to notice the hemorrhage (*e. g.*, in battle) is an unconquerable weakness which deprives the patient of muscular power and forces him to be completely passive. The general weakness then becomes evident in tremor on voluntary movement, and feebleness of the voice. If the loss of blood continues, flashes of light, ringing in the ears, hallucinations of smell, and feelings of anxiety arise. A profuse cold sweat breaks out and the secretion of urine is

[1] The origin of acute post-hemorrhagic anemia by destruction of the red blood-corpuscles within the circulation will be discussed in the section on Hemoglobinemia.

increased. The pulse is of changing frequency and tension; the heart palpitates actively. On continuance of the hemorrhage the heart weakens, its sounds become feebler and less clear; the pulse smaller, less frequent, and readily compressible. The local anemia of the vital organs becomes evident; anemia of the brain is shown by singultus, nausea, vomiting, and even fainting. The syncopal condition, at first of short duration, alternating with waking, gradually becomes deeper and yields only transiently to a sort of half-slumber, during which aphasia, paraphasia, and delirium set in.

The defective perfusion of the lungs with blood is shown by a marked dyspnea. The pulse becomes small and feeble and gradually impalpable.

Later, terminal symptoms develop referable to the loss of fluid. The sweat disappears, the skin becomes flabby and dry, the eyes lusterless, the voice almost inaudible. Fibrillary muscular contractions, spasms of individual muscle-groups, of single extremities, eventually general convulsions, occur. If the pulse is still palpable, it is intermittent and less frequent. The respiration is slowed and usually superficial. The body feels cold, and the thermometer shows, even in the body cavities, less than 32° F. The pallor of the skin changes to an ashen yellow. Death is at hand.

The hemorrhage may cease at any stage, either spontaneously or artificially. Under these circumstances the further course, the possibility of recovery, and the duration of convalescence depend on the amount of blood lost. Still there are limits beyond which the hemorrhage is necessarily directly fatal even when it has been checked before death has actually occurred. Moreover, though these statements are only approximate, it may be affirmed with certainty that an adult will not recover from the loss at one time of more than half his entire blood (Panum). The results of the numerous experiments on animals (see later) (Feis, Maydl) in regard to this point can not be immediately applied to man because different species of animals show very different powers of resistance to hemorrhage. General experience would seem to show, however, that man can stand the loss of a greater percentage of blood than the majority of experimental animals. If the hemorrhage is checked before a fatal amount is lost, the patient is yet in great danger during the days immediately following. The disease-picture is then dominated by an intense weakness which may make the slightest active movement impossible. The functions of almost all organs are depressed, and in the majority of cases we find important alterations which require a separate, more accurate description.

SYMPTOMATOLOGY.

Alterations of the Blood and of the Bone-marrow.—Interest is attracted first to the alterations manifested by **the blood** as a result of its loss in quantity.

As mentioned previously, all authorities agree that there is an immediate increase in the watery elements of the blood after a moderate hemorrhage—*e. g.*, 50 to 100 c.c. Following slight losses of blood, therefore, there is no diminution of the amount of fluid in the vessels; in other words, no pure oligemia. Since we have no accurate method of making such observations, it can not yet be stated with certainty whether the amount of blood is diminished for any considerable time even after copious hemorrhages. After violent, immediately fatal, hemorrhages a marked diminution of the amount of blood naturally occurs, since the replacement of fluid from the tissues naturally requires more time than the actual hemorrhage. Such cases, therefore, show on section extremely small amounts of blood in the vessels.

Following slight and moderately severe hemorrhages the lost blood is so rapidly replaced by fluid from the chyle and lymph-vessels and the tissues that the eventual difference in the amount of blood bears no relation to the severity of the hemorrhage.

This replacement of the fluid by other tissue-juices necessarily leads to considerable qualitative alterations of the blood. The most conspicuous of these is the increase in the quantity of water in the blood, the **hydremia.** This is demonstrable by the specific gravity, the quantity of dried substance, and the percentage by volume of red blood-corpuscles, and it is the more marked the greater the hemorrhage.

According to Herz, v. Jaksch, Dunin, this increase in water affects especially the red blood-corpuscles, while the serum is comparatively little altered in its composition. E. Grawitz and Hammerschlag, on the contrary, refer the hydremia of the blood in post-hemorrhagic conditions, particularly to an increase of water in the serum.

The investigations of M. Herz especially tend to show an increase of water in the red blood-corpuscles, and it was in cases of post-hemorrhagic anemia that he first described the "acute swelling of the blood-discs." He found, for instance, in one case of hematemesis seven to ten hours after the hemorrhage, 900,000 red blood-corpuscles (instead of the normal 4,500,000), and their percentage volume (estimated by the hematocrit) 28 per cent. (instead of the normal 40 to 50 per cent.). From this Herz reckoned that the average volume of the individual corpuscles, which normally amounts to 800 to 1000 (sc. $\frac{1}{10000000000}$ cm.), had increased to 3069.

This observation can be explained only by assuming that the blood-cells were markedly swollen by the taking up of water.

The further course of this case is remarkable. Nine days later the number of red blood-corpuscles was 1,040,000, the entire volume 12 per cent., when the average volume of the individual cells would be 1053. This result, therefore, indicates that a swelling still existed even though the numbers were much nearer normal.

The material at hand concerning the diminution in the **number of blood-corpuscles** and in the absolute and relative **amount of hemoglobin** is much richer. A mathematical ratio between this qualitative diminution and the amount of blood lost can not be expected, as is evident from Vierordt's animal experiments, in which the diminution in the number of blood-corpuscles was relatively less the greater the loss of blood. Still, these figures represent the most accurate expression of the existing alterations.

The following example (F. A. Hoffmann) of a pretty copious venesection may act as an introduction to the writer's remarks: 425 gm. of blood were taken from a robust man of 84.46 kg. weight with 5,219,000 red blood-corpuscles per c.mm. and 15.14 hemoglobin per 100 gm. blood. One-half hour later the number of blood-corpuscles was 4,762,000, the hemoglobin 13.63; one day later, 4,681,000 and 13.41. If the blood is reckoned as one-thirteenth part of the body weight, 6 per cent. of the entire amount of blood was withdrawn, yet the diminution of the corpuscles and the hemoglobin amounted after half an hour to about 10 per cent., and the next day to even more. We can naturally only conclude that the amount of blood lost was measured exactly, and that the other figures, therefore fluctuate within more or less wide limits.

[Regarding the dilution of the blood consequent upon hemorrhage the editor quotes the following from his discussion of the subject:[1]

"Liquid is in some way absorbed by the blood, and the ready explanation that the vessels are filled by the juices of the various tissues is at hand. There is not, however, a mere dilution with water, as chemic analyses readily demonstrate. For example I would quote the following experiment:

"A small dog weighing 16 kilos, was bled from the jugular vein, one-third of his total blood (estimating the total quantity at one-thirteenth of the body weight) being removed. Before the experiment the following values were determined: red blood-corpuscles, 6,900,000; white blood-corpuscles, 42,000; specific gravity of blood, 1095.9; specific gravity of serum, 1022.8;

[1] *Jour. Amer. Med. Assoc.*, July 24, 1897.

dry residue of blood, 23.2 per cent.; dry residue of serum, 7.4 per cent. Ten minutes after the bleeding, small quantities were taken for examination and the following results obtained: red blood-corpuscles, 6,610,000; white blood-corpuscles, 19,600; specific gravity of blood, 1055.9; specific gravity of serum, 1022.6; dry residue of blood, 21.6 per cent.; dry residue of serum, 6.9 per cent.

"It will be noted that there was no immediate change in the quantity of blood; at least no striking change. Seven hours after the bleeding the following figures were obtained: red blood-corpuscles, 2,615,000; white blood-corpuscles, 20,600.

"Chemic analyses were not made at this time, but were carried out at the next examination, forty-eight hours after the original bleeding. The animal was again etherized and blood removed from the femoral vein: red blood-corpuscles, 3,100,000; white blood-corpuscles, 26,000; specific gravity of blood, 1046.7; specific gravity of serum, 1022.1; dry residue of blood, 10.47 per cent.; dry residue of serum, 7.4.

"From the similarity in the blood-count at this and the previous examination, the writer assumes that the dry residue of the blood and serum would have been found practically the same at the previous examination. It is evident then that the mass of the blood is soon diluted after hemorrhage, and the diluting fluid is approximately the same in density and probably in character as the original plasma. This is shown by the preservation of the normal conditions of the serum while the total blood has undergone diminution in weight and in solid residue.

"The manner in which this change occurs is of very great physiologic interest, and bears important relations to the etiology of anemia. Either there is a direct transfer of the liquids of the body to the vascular system through the walls of the vessels, and a depletion therefore of the general system in favor of the blood, or there are active secretory processes affecting the vessels, according to the theory of Heidenhain."—ED.]

That the amount of hemoglobin and the number of corpuscles reached their lowest figure not immediately after the hemorrhage, but only some time later, is an observation that has been frequently confirmed, and this decrease continues longer and reaches lower figures the larger the hemorrhage. The reason for this is clear. The increase of corpuscles and fluid from the tissues takes place gradually; the thinning of the blood, therefore, progressess for a long time after the hemorrhage, producing a further decrease in the relative numbers. In addition to this, according to Ehrlich, the hydremia produces a rapid destruction of the least resistant erythrocytes.

Practical and accurate methods have enabled the writer to estimate the limits to which the percentage of hemoglobin and number of corpuscles may sink without proving fatal. Vierordt affirmed after experiments on animals that a decrease in the number of corpuscles to 50 per cent. was fatal, but this has been proved false in animals (Buntzen, Gurber), and even more in man. Laache described several cases where the number of corpuscles sank below 50 per cent., and one especially

in which the number was only 32 per cent. of the normal. Béhier observed after a metrorrhagia a diminution to 19 per cent., with complete recovery. The lowest percentage with recovery in an acute anemia was observed by Hayem in the case of a woman who had two severe puerperal hemorrhages within six days, and manifested fifteen hours after the second hemorrhage a diminution in the blood-corpuscles to about 11 per cent. of the normal.

The *progress of recovery* is also most evident from the percentage of hemoglobin and the number of red blood-corpuscles. As a rule they reach their lowest mark one to three days after the hemorrhage, though sometimes somewhat later, up to seven days. Siegl and Maydl observed the minimum after severe hemorrhages between the fifth and eleventh day. The percentage of hemoglobin experiences a greater decrease than that of the red blood-corpuscles. Moreover, in recuperation the two do not run parallel, but the former lags considerably behind the latter. This remarkable phenomenon, for which we have seen an analogy in the discussion of the influence of altitude on blood-formation (see page 22), may be expressed in other words, namely, that the individual corpuscles fail to obtain their full quota of hemoglobin during this stage of restitution. This is partly explained by the fact that a large number of corpuscles do not attain normal size, many smaller forms, even microcytes (see below), being almost regularly seen. Still this explanation does not apply to all cases, since microcytes are sometimes entirely wanting (Laache). In these cases we must assume with Laache that the corpuscles discharged by the blood-making organs are poorer in hemoglobin than is normal.

Laache has shown this phenomenon in a very instructive curve (see Fig. 5). This is from a case of severe anemia produced by a complicated fracture of the leg in a previously healthy sixteen-year old girl. The narrow line shows the gradual increase in number of red blood-corpuscles from 1,400,000 to the normal within about two months. The broad line shows the number of corpuscles corresponding to the amount of hemoglobin in comparison with the normal. On December 16, for instance, 5,200,000 red blood-corpuscles per c.mm. were found, but these were so deficient in hemoglobin that they correspond only to 3,600,000 normal blood-corpuscles. The elaboration of hemoglobin, therefore, remained considerably behind the new formation of blood-corpuscles.

Morphologic alterations in the blood-cells are likewise noticeable after an acute hemorrhage. In the case of the *erythrocytes,* for instance, normoblasts are found after every severe hemorrhage, from the second or third day to the completion of regeneration, provided the blood is examined sufficiently frequently, namely, once or twice daily. Usually

1880 October *November* *December*

Fig. 5.

that a hasty glance may produce the impression of a leukemia, especially when normoblasts are simultaneously present.

When a hyperleukocytosis occurs during an acute anemia, it is of short duration, and usually terminates with the restoration of the red blood-corpuscles and the hemoglobin.

In a small number of cases the proportion of the different white blood-corpuscles is altered in favor of the lymphocytes, which is readily explained by the increased activity of the lymph circulation. [In one of the editor's cases the differential count was as follows: Polymorphonuclear, 43.5 per cent.; lymphocytes, 27.1 per cent.; mononuclear, 16.4 per cent.; transitional, 10 per cent.; eosinophiles, 2.8 per cent. Cabot refers to a case in which the lymphocytes numbered 69 per cent., and the polymorphonuclear only 28 per cent.—ED.]

The writer had the opportunity of observing in one patient, who suffered from a moderately severe traumatic hemorrhage (wound of the liver), an exceptional and remarkable phenomenon. Preparations made six days after the accident showed, besides a pretty marked poikilocytosis and isolated normoblasts, a large number of myelocytes. These constituted 13.7 per cent. of all the white blood-corpuscles, with a proportion of whites to reds of 1 : 650. Three days later no trace of myelocytes could be found in the blood and, omitting one normoblast, nothing abnormal was seen.

Another very rare occurrence observed by Ehrlich in a severe case of post-hemorrhagic anemia may also be mentioned. He found the polynuclear cells entirely free of granules. He explains this phenomenon by assuming that the organism lost its power of producing neutrophile substances on account of the severe loss of blood.

The origin of this post-hemorrhagic leukocytosis has been variously explained. According to Virchow, it is to be attributed to the fact that the white blood-corpuscles, on account of their adhesiveness, do not so readily leave the vessels. Again, the first result of the loss of blood, namely, the dilution of the remaining blood by chyle and lymph, which are free from erythrocytes but rich in colorless cells, naturally influences the proportion of the white to red in favor of the former. Ehrlich considers it due to irritation of the bone-marrow. [In this connection the seemingly paradoxic result of bleeding in chlorosis may be considered. Numerous observers have found that the repeated abstraction of small amounts of blood sometimes exercises a beneficial effect in the treatment of chlorosis. Various explanations have been offered to explain this result, among which an important one is that which attributes the improvement of the blood to a stimulation of the bone-marrow.—ED.]

EXPLANATION OF PLATE I.

FIG. 1.—PREPARATION FROM AN ACUTE POSTHEMORRHAGIC ANEMIA DURING A BLOOD CRISIS.

a, Normal red blood-corpuscles: the pale ones contain less hemoglobin; *b*, normoblasts: *b*, normoblast with polychromatophilic protoplasm; *c* and *c*,' normoblasts showing the nucleus in the act of leaving the cell; *d*, free nuclei of normoblasts; *e*, lymphocyte; *f*, polynuclear leukocyte.

FIG. 2.—PREPARATION FROM A VERY SEVERE SIMPLE CHRONIC ANEMIA IN A CASE OF TERTIARY SYPHILIS.

a, Red blood-corpuscles showing marked polychromatophilic degeneration; *b*, blood-corpuscles showing extreme oligochromemia—"Pessary forms"; *c*, microcytes; *d*, blood-platelets; *e*, polynuclear leukocytes; *f*, large mononuclear leukocyte.

The drawings were made from preparations fixed in absolute alcohol and stained with Chenzinsky's fluid. Microscope: Leitz, Oil-immers. $\frac{1}{12}$, Oc. I, Tube-length 16.

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PLATE I.

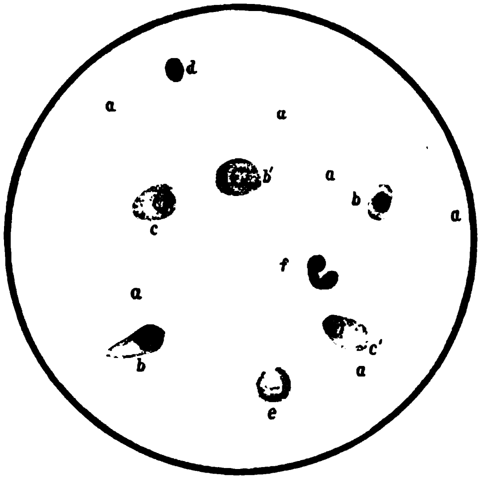

Fig. 1.

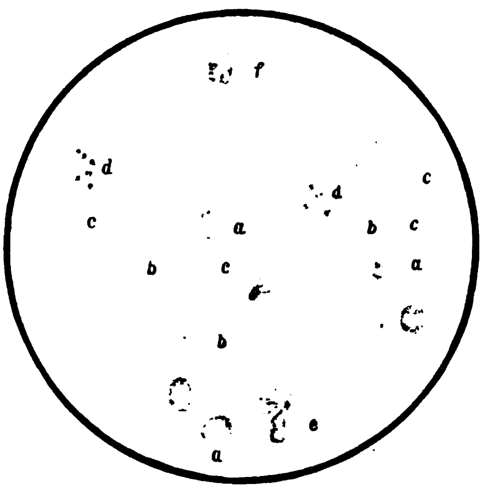

Fig. 2.

As a matter of fact, each one of these factors may participate. Special cases like that mentioned above, in which myelocytes occurred in large numbers, are only to be explained by Ehrlich's assumption.

Another important alteration which takes place immediately after the hemorrhage and is sometimes active in checking it, is an **increase in coagulability.** According to E. Freund's investigations, the time of coagulation may be hastened from nine to three minutes by hemorrhage. The writer has mentioned in another place Hayem's observation which stands in close relation to this fact, namely, that the blood-platelets are markedly increased in post-hemorrhagic anemia.

The alterations which the **bone-marrow**, especially that of the long bones, undergoes after severe hemorrhage must not be omitted. From animal experimentation (Litten and Orth) and occasional autopsies, we know that a few days after the hemorrhage the fatty marrow is transformed to red marrow and contains enormous numbers of nucleated red blood-corpuscles; in other words, normoblasts. This metamorphosis gives the key to the clinical morphologic alterations of the blood just described, namely, the appearance of normoblasts and the occasional occurrence of hyperleukocytosis.

ALTERATIONS IN THE GENERAL CONDITION AND IN THE INDIVIDUAL ORGANS.

These alterations in the blood give to the general picture its striking symptom, namely, the pallor of the **skin and of the mucous membranes.** In acute anemic conditions this manifests a peculiarity not only of degree, but also of color, by which it is differentiated from the pallor of chronic conditions. The color, unlike that in chronic disease, is not yellowish, but whitish, and resembles much more the color which we see under severe psychic excitement, as shock, fright, and the like. This difference in the color of the skin attracts attention even after hemorrhages in persons previously anemic and very pale—*e. g.*, a gastric or duodenal hemorrhage in a chlorotic patient.

The tendency to slight *edema*, especially about the malleoli, must be attributed to the hydremia. This edema occurs even with the horizontal position, and is almost always seen when with the recurrence of strength the patient walks about for the first time. It is undoubtedly independent of albuminuria, since it also appears when no trace of albumin can be found in the urine. Whether, as Cohnheim affirms, a permeability of the vessels is to be made responsible, or whether the abnormal chemic composition of the blood itself creates other conditions under which transudation may occur, can not be stated with certainty.

Fischl first, and later Quincke and many others, described an **albuminuria** after very severe hemorrhages. In rare cases it appears several hours after the hemorrhage and reaches a pretty high grade. Microscopically the urinary sediment shows only isolated hyaline casts and kidney epithelium, but no signs of renal inflammation. At the autopsy on a patient who succumbed immediately after repeated hemorrhages, all of which took place within twenty hours, and whose urine showed considerable amounts of albumin, Quincke was able to demonstrate that the kidney epithelium was completely uninjured. In spite of this, it seems justifiable to refer the abnormal excretion of albumin to lesions of the kidney epithelium, which are produced by the severe circulatory disturbance and the defective nutrition, yet are not demonstrable microscopically. Still, the watery composition of the blood creates other conditions of diffusion which may be capable of producing the passage of albumin into the uriniferous tubules. It may even be possible, as Quincke suggests, that the albuminous material passing into the blood from the tissue-juices is not completely identical with serum-albumin, and, therefore, produces an irritation of the kidneys which leads to an abnormal permeability.

Except this occasional albuminuria, no other abnormal constituent is found in the urine in traumatic anemia. The urine is pale, and its daily amount is, as a rule, increased. This is naturally not to be attributed to the disease-process *per se*, but rather to the copious ingestion of fluid resulting from the intense thirst.

The changes in **metabolism** in acute hemorrhage have been the subject of numerous experimental investigations. On the basis of the early experiments of Bauer it was long assumed that the *processes of oxidation* are diminished. Still further animal experimentation (Grüber) has shown that the consumption of oxygen itself is no less than in health, at least as long as the physical essentials to the circulation are preserved or are replaced by a suitable fluid substitute. v. Jürgensen called attention to the fact that with an absolute diminution of the functional capability of the hemoglobin, the organism preserves its physiologic activity by an increase in respiratory frequence and cardiac energy; while F. Kraus found from his experiments that not the frequency but the depth of the respiration underwent an increase.

In addition to these two factors, we have poikilocytosis (previously considered in regard to this same point), which so distributes the hemoglobin present that it offers an increased surface, and is thus capable of meeting the greater demands.

There is likewise a lively contradictory discussion in relation to

albuminous decomposition in acute anemia. Bauer found after the withdrawal of a considerable amount of blood from a dog, the excretion of nitrogen increased to 30 per cent. and over; and Kolisch reports a case of severe post-hemorrhagic anemia with ulcus ventriculi in which there was a marked increase in the excretion of nitrogen, amounting to about three times the amount ingested; moreover, according to the same authority, Neusser found in a similar case even five to six times the amount of nitrogen. v. Noorden reports, however, two cases of dangerously severe gastric hemorrhage which neither on the day of the hemorrhage nor subsequently excreted more nitrogen than would correspond to the amount ingested.

In all forms of severe or long-continued anemia, especially in anemias following a single severe or repeated hemorrhage, **fatty degeneration**, particularly in the circulatory system, has been observed (Ponfick). In mild cases this affects the connective-tissue cells of the intima of the larger arteries and of the endocardium; in severe cases the heart-muscle itself. Perl found in dogs after the withdrawal of blood by repeated venesection at long intervals the cardiac musculature, especially the papillary muscles on the left side, sometimes devoid of cross-striations and the sarcolemma filled with fat-droplets. In cases in which the hemorrhage is followed by death after some days, more or less fatty degeneration is found also in the capillaries, especially of the brain, and in the glandular cells of the liver, stomach, and renal cortex.

The older writers attributed this fatty degeneration to the diminished oxidation brought about by the anemia. More recent investigations (Kraus, Thiele, and Nehring) not only unanimously contest the occurrence of a diminution of the oxygen consumption, but also assert that there is an augmentation of it in comparison with the normal. Still it would be hasty to dismiss the above-mentioned explanation before another sound one is proposed; for the statistics at our disposal are obtained from the gas metabolism of the entire organism, and they naturally do not show the variations which might take place in individual organs.

That in conditions of severe acute anemia the heart and the vessels occupy a unique position is evident from the fact that the functions of all other organs are decidedly depressed, at times almost wanting; while the activity of the circulation continues; in fact, the sum total of its activity may be increased in comparison with the normal. The organism as a whole can, therefore, be sufficiently provided for, while the metabolism of individual parts is defective. An analogous occurrence for which this explanation is appropriate is presented by the

ocular muscles, which, according to A. Fränkel, may degenerate in pernicious anemia in the same way as the cardiac musculature.

As a result perhaps of the fatty degeneration of the vessels there is a decided **tendency to spontaneous hemorrhage.** Hemorrhages from the gums, from the nose, from the uterus, and into the retina may give rise to severe complications and seriously retard the general restoration.

In considering the disturbances of the **circulation** in acute anemia, we must first describe those produced immediately by the hemorrhage. Observations on man have been naturally made only within the narrowest limits, yet careful animal experimentation has taught that on a rapid withdrawal of a large amount of blood the arterial pressure rapidly sinks and the pulse becomes small and compressible. If the hemorrhage ceases, the arterial pressure returns to normal in a few minutes, and, according to Cohnheim, dogs stand the loss of more than one-fourth the entire amount of blood without any persistent reduction of the arterial pressure. This is brought about by automatic regulation in that the vasomotor center is readily stimulated by the anemia and so re-establishes the necessary pressure by contraction of the vessels. Moreover, if by the introduction of fluid from the tissues, the contents of the vascular system are restored to their original amount (a process which takes place very rapidily), the old tension is approached.

After the hemorrhage, during the development of the anemic condition, several disturbances of the mechanics of the circulation are to be noted which can be demonstrated on a careful study of the pulse. The damage suffered by the heart in the greater or less fatty degeneration of its muscle has been stated before. These anatomic changes explain the persistence of a pronounced debilitas cordis, even after the disturbances of the composition of the blood have been fully compensated for. The entire heart action is more feeble, the heart-sounds are weak and frequently associated with or replaced by characteristic accidental murmurs. The pulse remains very feeble for weeks, even after it has become of its normal volume. The often-occurring slight alteration in frequency is especially characteristic. During the first few days after the hemorrhage an energetic movement in bed may produce violent palpitation of the heart and suddenly increase the frequency of the pulse; in later stages the same effects, or even sometimes conditions resembling collapse, are produced by relatively trifling causes—*e. g.*, a change between lying and sitting, an evacuation of the bowels, or even slight psychic emotion. We have, in fact, a condition which closely simulates that occurring in the convalescence of certain infectious diseases, especi-

ally the intoxications. Moreover, we see after severe hemorrhages, as well as after diphtheria or typhoid fever, pitiable cases where the convalescent, animated by the feeling of fully restored health and strength, makes too great a muscular effort, such, for instance, as leaving the bed too soon, and succumbs to a cardiac paralysis (Immermann).

The functional activity of the **digestive organs** is likewise reduced to the lowest level. Immediately after the loss of blood from the vessels a burning thirst usually sets in, the satisfying of which helps to compensate for the loss in fluid suffered by the body. The desire for food is, on the contrary, primarily depressed, and the power of absorbing food, especially solids, is markedly lowered, so that diet demands the most careful watching both in regard to amount and quality. Moreover, this must be exercised more scrupulously in the further stage of convalescence, since a voracious appetite usually comes on which induces the patient to put more work on the digestive organs than they can stand. Manassëin found experimentally, in dogs from which he removed by repeated venesection one-third to one-half of the entire amount of blood within four days, that the gastric juice possessed much less power of digestion than under normal conditions, though by the addition of hydrochloric acid he was able to raise it to the normal. On account of the great indulgence required by patients with acute anemia the clinical observations are naturally extremely scanty. Kolisch recently examined a patient with a severe subacute post-hemorrhagic anemia which proved fatal, and found a copious amount of free hydrochloric acid in the stomach.

For the same reasons no exact examinations are at hand on the absorptive activity of the intestine; yet from the clinical course in persons previously healthy, and the extraordinary rapid restoration of strength, it is to be assumed that the ingested nourishment is completely absorbed.

Scagliosi recently observed anatomic alterations in the **central nervous system,** which from the report of the case can only be regarded as a result of the severe loss of blood. The patient was a gravid woman, who suffered severe losses of blood at intervals for about thirty days, and during labor succumbed. The brain showed decomposition and solution of Nissl's bodies; the spinal cord, especially in the anterior horns, exhibited marked atrophy of the ganglion cells and enlargement of Nissl's bodies, associated with a diminished power of staining. Scagliosi reports no clinical symptoms which would correspond to the anatomic changes.

In the description of severe hemorrhage mention has been made

that *hallucinations* and *delirium* may appear as a result of the anemia and constitute a threatening if not terminal symptom. Still no reports can be found in the literature of persistent psychoses which were undoubtedly due to a severe loss of blood (Krafft-Ebing).

Hallervorden observed several cases of acute anemia accompained by transitory *disturbances of speech*, which, according to his description, can be attributed only to the loss of blood, and not to any allied circumstance like fright, rupture of vessels, etc.

The speech in this case was anarthric, and simulated that of intoxication or bulbar paralysis. The aphasia in connection with it was both motor and sensory. Hallervorden mentions as especially characteristic that the intensity of the symptoms depended on the position of the body or the momentary condition of fatigue. These disturbances are most readily attributed to an anemia of the nuclei in the medulla oblongata or of the cerebral cortex. The prognosis seems to be absolutely favorable.

A rather rare result of marked loss of blood is neuralgia. It is seen especially in the cerebral nerves, and is extremely severe and obstinate.

As in all anemic conditions, so too in the post-hemorrhagic, a prominent place is taken by **ocular complications.** Knies insists that amblyopia and amaurosis do not occur after loss of blood in persons otherwise completely healthy, and that an added factor is necessary. In illustration of this he states that not a single case of this kind was observed in the whole campaign of 1870–71. Still observations are not rare, and a very large number of them seem to have been made in cases of hemorrhages from the digestive tract, especially hematemesis. A clear picture of the mechanism of such visual derangement is not difficult to draw. When, for instance, the blood-pressure suddenly sinks in the whole vascular system, while the independent intra-ocular pressure remains normal, the circulation of the blood in the retina is naturally made more difficult. This may produce momentary disturbances of sight ("Schwarzsehen"), which rapidly disappear with the restoration of the general blood-pressure. Still, if the circulation of blood in the retina remains disturbed for some time, and a disease of the vessels of the optic nerve already exists, unilateral or bilateral derangements of vision to even complete blindness may occur, either early or, as is usually the case, several days later. That these visual disturbances frequently occur not immediately, but a week or more after the hemorrhage, is explained by the assumption that during the ischemia degeneration of the delicate vessel-walls takes place, especially if they

were not entirely intact before. On the restoration of the blood-pressure then we have rupture of continuity and hemorrhage (Knies).

The ophthalmoscopic finding, even with comple amaurosis, may be negative, or there may be only a pallor of the papilla.

According to Schmidt-Rimpler, recent cases usually show a neuritis, or sometimes a neuroretinitis with isolated hemorrhages. When the amaurosis persists, atrophy of the optic nerve results. Hirschberg and Rothmann describe in such cases a delicate edema about the optic nerve. Schmidt-Rimpler reports in another volume of this system hemorrhages into the vitreous humor after a violent epistaxis.

The prognosis of the visual disturbances after hemorrhage is very dubious, and in no way directly dependent on the severity of the hemorrhage. Even complete amauroses are usually only transitory, though they may leave behind slight persistent derangements. Yet cases of incurable amaurosis or persistent severe amblyopia have been not infrequently observed.

[W. C. Posey [1] has studied the condition of the eyes in cases of secondary anemia. He notes that, as most of his observations were in adults who had been exposed to many causes which might produce ocular lesions, it was impossible to exclude this from the results of anemia. In many cases, however, of anemia resulting from heart and stomach disease, he found pallor of the discs, narrowing of the vessels, and lighter blood columns, which were evidently conditions produced directly by the anemia. In the majority of cases of anemia, however, even where there was a marked reduction in the blood count, the fundus of the eye was perfectly normal.—ED.]

DIAGNOSIS.

The diagnosis of a severe acute anemia presents not the slightest difficulty. The problem of discovering the seat of an internal hemorrhage, the chief symptoms of which are presented not by the anemia, but by the local disturbances, is not to be solved here, where we have to do merely with the recognition of the anemic condition *per se*. This is characterized by symptoms like general weakness, pallor, a tendency to fainting, and the small size, compressibility, and changing frequency of the pulse, which are so striking that the occurrence of a severe internal hemorrhage could escape even the inexperienced only through the greatest carelessness. From a differential diagnostic point of view, all acute disturbances in the distribution of the blood, such as are seen under different nervous influences, can come into consideration, namely, fright, anxiety,

[1] *Jour. of Amer. Med. Assoc.*, July 24, 1897.

and severe psychic shocks. Excesses in baccho et venere can also produce such marked changes in the distribution of the blood as to give rise to the thought of a true anemia ("vascular anemia," Quincke). An accurate examination, especially of the heart's action which is undisturbed, of the pulse which is of proper size and tension, and, above all, the transitiveness of the symptoms, indicate the correct diagnosis. A morphologic examination of the blood in such cases would be of little value, because the histologic changes peculiar to acute anemia are found, at the earliest, twenty-four hours after the hemorrhage. Still, the determination of the number of corpuscles and the percentage hemoglobin would be occasionally of service.

PROGNOSIS.

The termination of an acute post-hemorrhagic anemia in a previously healthy, robust individual is almost always in complete restoration; in fact, sometimes, as after acute infectious diseases, the person appears more robust and healthy than before the hemorrhage.

As far as the possibility of recovery is concerned, we must look first to the cause which produced the hemorrhage and the complications arising with it. If the anemia is the result of a trauma which in itself puts no difficulties in the way of recovery, restoration to normal is very likely. Every complication, whether present in the cause that produced the hemorrhage or appearing later, retards the course of reparation or may prevent it entirely.

How great a loss of blood is consonant with anticipated restoration is a question of considerable practical import, and one on which great attention has been bestowed by many investigators, especially surgeons, in connection with hemorrhages in operations. Statistics are naturally incapable of giving exact ideas on this point. Moreover, the results of animal experimentation are not conclusive in connection with human conditions, for, among the different animals, there is a marked difference in susceptibility to hemorrhage. The best criterion, even though it is very unsatisfactory, by which the different cases may be compared with one another, is not the amount of blood lost, but the number of red blood-corpuscles per c.mm. remaining. In general, we may assume that a healthy man can lose rapidly one-half his blood and more and still be capable of recovery. The decrease in the number of red blood-corpuscles can be even greater, for, as mentioned in another place, Hayem reports a case in which the number of red blood-corpuscles sank quickly to 11 per cent. of the normal and yet recovery followed.

According to the size of the hemorrhage, the duration demanded by

the regeneration of the blood varies. How long a time will be consumed before the hemoglobin and the number of blood-corpuscles again become normal is primarily dependent on the amount of blood lost. Still, individual differences and the condition of the patient before the hemorrhage play a decided rôle. Individuals in the prime of life and in complete health replace losses of blood amounting to from one-third to one-half of the entire quantity in a few weeks, while feeble, sickly individuals or old people require as many months. Buntzen states actual figures on this point: In one case in which the diminution of red blood-corpuscles amounted to 23 per cent., the regeneration took eight days; with a diminution of 29 per cent., in one case ten, in another thirteen days; and in one case, with 39 per cent. loss, thirty-four days.

Bierfreund has constructed the following table to indicate the rapidity of regeneration after hemorrhage:

Loss of blood in hemoglobin.	Male.	Female.	Age (years).						
			1–10	10–20	20–30	30–40	40–50	50–60	60
10–15 per cent.	12.7 days	17.1 days	20.0	13.2	10.8	10.4	16	17.0	
16–20 "	17.9 "	23.5 "	21.0	19.0	12.5	16.2	21	22.7	23.8
21–25 "	20.3 "	23.5 "	22.5	21.3	17.6	. .	19	28.0	27.0
26 "	27.0 "	31.3 "							

In this regard there seems to be no difference between the sexes; at least the observation found in many text-books that females show a greater tolerance to severe losses of blood is not substantiated; in fact, from Bierfreund's statistics, the opposite seems true.

According to Schiff, the newborn require an exceedingly long time for the restoration of hemoglobin and blood-corpuscles. Several diseases, particularly tuberculosis and malignant tumors, according to Bierfreund, retard regeneration; while, strange to say, tertiary syphilis and benign tumors have absolutely no influence.

In regard to certain therapeutic measures, one should not forget Bierfreund's observation, that the restitution of the blood occurs no more rapidly (though likewise no more slowly) when the hemorrhage is subcutaneous or into the tissues than when it is external. If the effusion of blood is unfavorably localized, for instance, in the peritoneal cavity, retardation, rather than acceleration of recovery, is to be anticipated.

Many clinical and experimental observations show that after a hemorrhage that is not extremely severe regeneration may result in a a greater number of corpuscles than were present previous to the hemorrhage.

Though the prognosis of acute anemia is as a rule very favorable,

uncomplicated cases are sometimes observed in which a complete restoration fails to take place and a chronic anemia results. These are cases in which the hemorrhage was extreme and affected the blood-making organs so severely that they were unable to regain their full functional power. In the chapter on Progressive Pernicious Anemia, cases will be reported in which the origin of this disease can be attributed with great probability to severe acute hemorrhages.

The course and the termination of complications affecting individual organs are often entirely independent of the course of the anemia; this may disappear, that persist, and *vice versa* (compare what is said in the special sections).

TREATMENT.

Arrest of Hemorrhage.—The methods of arresting hemorrhages are chiefly treated in the text-books on surgery and obstetrics. Moreover, depending on the cause, such different methods are employed in case of hemorrhage from internal disease that the writers must leave their discussion to the special sections on internal medicine, such as those on phthisis pulmonum, ulcus ventriculi, and typhoid fever, and be contented here with the general treatment of internal hemorrhage.

The first requirement for the checking of hemorrhage is absolute rest. In many cases the patient is quiet involuntarily on account of the weakness which comes on so rapidly; still not infrequently rest must be forced even by the aid of narcotics—opium, morphin, codein—especially when an intense cough, violent pain, psychic excitement or hallucinations (see above), which really call forth a renewal of the hemorrhage, demand it.

Among the remedies producing arrest of hemorrhage on internal or subcutaneous administration may be mentioned especially liquor ferri sesquichlorati, lead acetate, secale cornutum, ergotin, stypticin, and hydrastis canadensis. According to the personal experience of individuals the opinions as to the value of these remedies differ widely, and authorities are not wanting who consider that an arrest of hemorrhage by medicaments is impossible. Nevertheless, the writer must say that he has frequently seen a favorable influence exercised, especially in hemotysis, by secale cornutum and ergotin.

[An important addition to our means of controlling hemorrhage by local application has recently been made to the pharmacopeia in the various preparations of suprarenal gland. Of these, the purified product adrenalin and its solutions are the most important. The direct application of a solution of adrenalin chlorid (1 : 10,000 to 1 : 5000) acts as a powerful hemostatic, and is applicable in the treatment of

hemorrhages from external surfaces or mucous membranes that can be reached from the exterior.

Even in parenchymatous and internal hemorrhages, however, adrenalin and similar products of suprarenal gland have been used, not only for their vasoconstrictive effect, but also because they are supposed to have some influence in increasing the rapidity of coagulation of the blood.—ED.]

Lately gelatin has been frequently recommended as a styptic. Poljakow reports good results from its employment by stomach or rectum, in 10 per cent. watery solution (200 c.c. three times daily), in cases of hemorrhage from the digestive tract. For subcutaneous injection, Davezac employs, and he claims with good results in the hemoptysis of phthisis, a solution of 2.5 gelatin in 100 physiologic salt solution, 5 to 10 c.c. being injected at a time. Curschmann injected subcutaneously several days in succession 200 c.c. of a sterilized gelatin solution, and claims that in 13 of the 14 cases observed of severe stomach, intestinal, and pulmonary hemorrhage, the hemorrhage rapidly ceased.

[The editor's experience with gelatin as a hemostatic has been confined to the treatment of hemorrhage in typhoid fever and of hemoptysis in pulmonary tuberculosis, in both of which he has used this treatment extensively. The conclusion reached after this experimenting has been that there was probably a moderate influence for good in this treatment, though the results were not so certain as might be desired.

In treating hemorrhage in typhoid fever gelatin was administered by the mouth as well as hypodermically, in order that the undigested gelatin might be carried along the intestinal tract to the seat of hemorrhage. Local applications of gelatin have been repeatedly used for the purpose of checking hemorrhage, and the employment of weak gelatin preparations by the mouth might therefore be advantageous in typhoid fever.—ED.]

The administration of common salt, Glauber's salt, and the like, which have been frequently employed in hemoptysis, though with not very assured results, is based on the experimental fact that the diffusion of large amounts of fluid into the intestinal canal produces a decided thickening of the blood (Grawitz).

It is likewise recommended in cases of persistent hemoptysis to ignore the thirst as long as possible. In cases where all medicaments failed, the writer has been more than once impressed with the favorable influence of this procedure. Whether remedies which, according to

Wright and others (calcium chlorid), increase the coagulability are of therapeutic value is difficult to prove, since, according to Freund, the hemorrhage itself is such a potent factor in the same regard. Yet if, as in the hemorrhagic diathesis, the diminution of the coagulability of the blood belongs to the nature of the disease, these remedies are of undoubted value in the checking of the hemorrhage.

[The investigations of E. A. Wright have showed the therapeutic value of calcium chlorid as a hemostatic, and this drug has been largely used in the treatment of various hemorrhagic diseases, and has even been administered by surgeons as a preparative treatment in conditions in which secondary hemorrhage is generally feared, such, for example, as in persons deeply jaundiced. Wright's experiments made with his coagulometer showed a decided decrease of the coagulation-time after the administration of calcium chlorid. This was true of healthy persons as well as of cases of hemorrhagic disease, such as hemophilia, purpura, etc. The effect of calcium thus administered seems to be temporary, and a continued use is not advisable.—ED.]

A final styptic which fulfils other important indications at the same time (see below) is the transfusion of blood or salt solution into the circulation. Cases have been observed in which this procedure was immediately followed by a cessation of the hemorrhage (F. A. Hoffmann). This apparently paradoxic fact is explained by assuming that the continuation of the hemorrhage is due to the atony of the vessels, which is rapidly removed by the sudden refilling of the circulation.

General Treatment of Acute Anemia.—After the first and most important essential in the treatment of a hemorrhage, namely, its control, has been accomplished, it is necessary to combat its immediate sequelæ. The greatest requirement is complete physic and psychic rest, and this should not be disturbed by therapeutic or diagnostic procedures which are not absolutely necessary. By lowering the head, warm covering, and cautious slaking of the burning thirst by hot or warm stimulating drinks, such as coffee, tea, or even small doses of alcoholic beverages, like sherry and cognac, the activity of the heart is stimulated and the tormenting sensation of general weakness somewhat lessened. If fainting occurs, or if the pulse becomes excessively frequent, small, or weak, stronger stimulants, like injections of ether and camphor, are indispensable. The objection has been raised against these remedies, which act so rapidly and intensely on the heart, that they may be the cause of renewal of the hemorrhage which has just ceased. Although such accidents have been observed, these remedies are indispensable in the treatment of threatening or actual collapse,

yet they are naturally to be employed only in the most absolutely threatening conditions.

A supply of heat must be carefully provided for by administration of hot drinks and the warm pack; in the later stages of convalescence the patients become cold very easily and demand these themselves.

Autotransfusion; Transfusion; Infusion.—Since the most serious result of a severe hemorrhage is the anemia of the vital organs, especially the brain and heart, it is obvious that the blood should be forced from the extremities, where it can readily be dispensed with, by firm bandaging and posture, into the trunk and head vessels (*auto-transfusion*). Still, if there is immediate danger, as shown by an impalpable or scarcely palpable radial pulse and irregular, slow, superficial respiration, there should be no hesitation in taking more active measures: either *transfusion*—*i. e.*, injection of blood from another individual; or *infusion*—*i. e.*, injection of physiologic salt solution or other fluid substitute (see below).

The immediate danger to life after severe hemorrhage is due (1) to the defective oxygen-supply in the organs, especially the brain and the medulla oblongata; (2) to an incomplete filling of the vascular system, which is compensated for neither by resorption of fluid from the tissues nor by a higher tension of the vessels, and finally leads to cessation of cardiac activity even when this is not paralyzed by the anemia of the medulla oblongata. Transfusion and infusion are employed for both these conditions.

The injection of fresh blood meets both the conditions best. The injection of salt solution readily fulfils the second, and perhaps partly aids in making up for the deficiency in oxygen by favoring the transport of actively functionating blood elements stored in the blood-making organs into the vessels.

A whole series of methods for the transfusion of blood have been proposed and rejected. The employment of animal blood was entirely given up when it was found that the serum of one species of animal had the faculty of breaking up the blood-corpuscles of another. The introduction of the blood of a healthy man may be accomplished intravenously or subcutaneously. The subcutaneous injection of defibrinated blood is much more simple, and is not associated with the dangers of intravenous injection, though its effect is not so rapid, and only a portion (still, according to Quincke, the greatest portion) of the blood passes over into the circulation so as to be functionally active, the rest remaining at the site of injection to undergo destruction.

In opposition to Quincke, the writer considers it doubtful that any

considerable part of the subcutaneously injected blood becomes functionally active. Moreover, Bierfreund's observations would support this, in that they show that the regeneration of the blood proceeds no more rapidly after a subcutaneous than after an external hemorrhage.

Against the extensive employment of subcutaneous transfusion is the circumstance that it is extremely painful, so that, according to Ziemssen, chloroform narcosis is absolutely necessary; and thus, in the majority of cases, would demand the most serious consideration.

Intravenous transfusion of blood is either direct or indirect. The former is made immediately from a vessel of the person giving the blood, best from an artery, into a vein of the recipient. The conduction is accomplished by glass cannulas tied in the blood-vessels, and joined by rubber tubing. Sometimes in this simple apparatus a small arrangement is introduced by which the amount of blood can be measured. A more accurate description is not required, since the danger of clotting, which can never be absolutely avoided (see below), strictly forbids its employment in man. Similar considerations have prevented the common practice of Ziemssen's method of intravenous transfusion of blood, though Ziemssen experienced no dangerous symptom in his own cases.

Ziemssen's procedure is as follows: A cannula with a rubber joint is placed in a vein of the person giving the blood and also into a vein of the recipient. By means of a syringe containing 25 c.c. the blood is transferred from one to the other. A second syringe in the hands of an assistant expedites the matter. Between the injections the syringe must be thoroughly cleansed with warm, sterile physiologic salt solution.

The great majority of transfusions are made indirectly—*i. e.*, the fresh blood is injected only after complete defibrination. The transference of clotted particles into the vein, which is unavoidable by the methods described, may produce direct occlusion of pulmonary arteries or their branches, or be the cause of new clotting within the blood-vessel. This danger is combated by injecting blood previously defibrinated whereby the functional activity of the red blood-corpuscles is not influenced. Yet even this method is not entirely free from danger, since severe symptoms of intoxication have followed its employment. According to Schönborn, these disturbances, which are attributable to the free fibrin ferment, may be avoided if moderate quantities (150 to 200 gm.) are transfused slowly.

The indirect intravenous transfusion of blood is accomplished as follows: The venesected blood (about 300 to 400 c.c.) is caught in a glass vessel, held in a water-bath at about 40° C. The blood is at once defibrinated by whipping with a glass rod or a stick till no more fibrillar material is

formed. In order to free the fluid entirely from clots, it is strained through a linen cloth directly into the funnel of the infusion apparatus. This consists of a large metal cannula with an olive-shaped head over which a tube is readily fastened, and the other end of this tube is drawn over the mouth of a small glass funnel. As in ordinary venesection, an arm vein is now constricted and the point of the cannula pushed directly into the vessel. The injection is made slowly; elevation and lowering of the funnel readily allow changes of pressure. It is obvious that the whole operation, even to its smallest details, demands the most painstaking asepsis.

Attempts to make the transfusion of fresh undefibrinated blood feasible by means of certain substances, such as the extract of leeches, which would render the blood incoagulable, have, as far as the writer knows, never been carried out on man.

In discussing the effect of blood transfusion, a separation into the momentary and lasting effect must be made. The former is often surprising. The pulse rapidly becomes full and strong, the respiration regular, and even the subjective improvement is marked. In brief, the collapse rapidly disappears. As is evident from corresponding observations with salt infusion, this result is due entirely to the introduction of fluid, and is, therefore, transitory, lasting often only a few hours. We can not readily decide whether the addition of foreign blood actually signifies anything toward an increase in functional capability. True, we know that the newly introduced red blood-corpuscles remain viable for some time, though many of them succumb subsequently, and even the primary increase in the percentage of hemoglobin soon falls. The "siderosis" of the internal organs, especially of the liver, found by Quincke after transfusion, points sufficiently clearly to the fate of the injected blood. The increase in hemoglobin and red blood-corpuscles, moreover, does not stand in a direct relation to the quantity of injected blood (Ziemssen), but remains considerably below it.

The many dangers of blood transfusion and the difficulty of finding a suitable person from whom to take the blood in the moment of danger, have resulted in its replacement by infusions of *physiologic salt solution*, especially since its absolute harmlessness, first demonstrated by Ponfick, has been continually confirmed.

The infusion of salt solution is made by one of the simple apparatuses described for the intravenous transfusion of blood. The solution should be injected at about the temperature of the body. In the containing vessel, therefore, it should be 5 to 10 degrees F. higher, since it undergoes considerable cooling in the funnel, the tube, and the cannula. The amount injected should be about 1 liter.

The subcutaneous injection of salt solution possesses no particular advantage over the intravenous, and, besides being very painful, does

not allow such a rapid introduction of large quantities. The infraclavicular regions are the most satisfactory sites for the injection.

A third method of administration of physiologic salt solution is *per rectum*. Warmann reports that 1 to 2 liters of the solution are completely absorbed within 4½ minutes, and that the results of this uncommonly easy method, which may be carried out at once without preparation, are not inferior to those of the infusion and subcutaneous injection. v. Mering likewise recommends this method most highly.

The experimental and clinical literature on this subject is extremely rich, and this is the best proof of the importance of the question. The older literature is found collected in Heineke and L. Lesser, the new in Feis and Schönborn. In spite of the great number of experiments, however, the question is still actively disputed. Investigators like Maydl, Feis, and others, refuse to recognize the glowing reports of clinicians as a proof of the value of the method. In their experiments on animals they were unable to find any degree of anemia in which it made any difference in the eventual termination whether an infusion of salt solution was employed or not; in fact, whether the animal in question lived or died depended entirely on the size of the hemorrhage and the individual resisting power. Although Feis was able to demonstrate graphically the very favorable influence which the injection of salt solution momemtarily exercised on the circulation and the respiration, since both, at least for a time, could be brought back to normal, yet this improvement was transitory, lasting only several minutes to several hours, and eventually the animals injected were in no way better off than the ones which had lost a similar amount of blood and had not been treated with the infusion.

Still, such a number of glowing results, especially in surgical and obstetric cases, can be contrasted with these experiments that the infusion of salt solution has come to possess an incomparably greater practical significance than transfusion of blood. Since it is without danger, it is possible that it has often been employed without strict indication, and that some happy results are unjustifiably attributed to it. Nevertheless, any one who has seen the transformation that infusion may cause in a patient whose pulse is scarcely or not at all palpable, whose respiration has almost ceased, and whose reflexes are abolished, is always ready, in spite of all experiments, to make the attempt again in a threatening case. Moreover, as demonstrated by Schönborn, cases occur in which the result of the infusion, at first transitory and replaced after a short interval by the old threatening condition, is permanent only after repeated injections.

[A. E. Taylor and C. H. Frazier[1] have studied the effects on the blood plasma of the saline transfusions following homorrhage. Their experiments were mainly directed to the determination of the amount of proteid and sugar in the plasma before and after transfusion. They found a rapid restitution of these important nutritive substances, and conclude that the flow of the lymph in the thoracic duct is too sluggish to account for the restoration, and that transfusion through the vessel walls could not occur to a sufficient extent to account for it, since the injection solutions were accurately isotonic. Hence, by inference they conclude that the proteid and sugar must have been derived from the tissues (liver, muscles, etc.) by direct lavage. The practical importance of these experiments is that they show the manner in which such transfusions may aid nutrition at critical times, not alone by restoring intravascular tension, but especially by the direct introduction into the circulation of nutritive materials.—ED.]

The attempt has recently been made to substitute for the solution improperly called "physiologic" salt solution, other fluids of varied composition. For instance, Schücking employed a solution containing 8 per cent. sodium chlorid and 0.33 per cent. sodium saccharate, and obtained from subcutaneous and intravenous injection magnificent results in several cases of severe acute anemia.

From the preceding the following may be taken as a summary:

(*a*) The indication for transfusion or infusion arises on the occurrence either of a hemorrhage which can not be checked by any other means or of a collapse-like condition following a severe hemorrhage in which the radial pulse is thready or impalpable, the respiration superficial and irregular, and the reflex irritability very much diminished or abolished.

(*b*) If the danger is so great that any delay may be fatal, we make a subcutaneous or intravenous or rectal injection of physiologic salt solution or sodium saccharate solution, and repeat it several times in case of a renewal of the collapse.

(*c*) If there is sufficient time, if everything is ready at hand, and a healthy man from whom to take the blood presents himself, the intravenous transfusion of defibrinated blood is to be done.

Dietetic Treatment.—If the patient has passed the danger of succumbing to the immediate effects of the hemorrhage, the therapy should be directed to promoting the efforts of the organism in the regeneration of the blood, and especially to the prevention of every circumstance that would disturb this process.

From what has been said as to the functional weakness of all the

[1] *Contributions of the William Pepper Laboratory of Clinical Medicine*, 1900.

organs in a severe acute anemia, it is obvious that every bodily effort should, as far as possible, be avoided. The importance of mental rest has been several times insisted on, and it must be reckoned on in the choice of a suitable sick-room, nurse, etc.

On account of the cardiac changes it follows that all muscular activity which might produce an immediate rise in the frequency of the pulse, or even mild dyspnea, must be avoided. Therefore, not only on account of a possible recurrence of the hemorrhage, but also on account of the danger of cardiac collapse, a physic examination, which would necessitate an upright or strained position on the part of the patient, should be entirely omitted or extremely limited.

Special attention must be paid to the time when the demand for absolute rest ceases and gives way to a feeling of renewed strength which does not correspond to the actual power, and may be the cause of dangerous accidents. From the first time the patient sits up till he leaves the bed and takes his first walk, the physician must see that no demands are made on the muscular power to which the heart responds abnormally.

The question of nutrition usually presents no difficulties unless the site of the hemorrhage (gastro-intestinal hemorrhage) demands special regulations. The tormenting thirst present immediately after the hemorrhage lasts at most one or two days, and is quieted by frequent small quantities of cool drinks or pellets of ice. The administration of large quantities of fluid after an internal hemorrhage must be avoided for fear of a recurrence or at least of a too sudden overloading of the circulation. In the beginning, the thirst should be taken advantage of to introduce nourishment, especially cool milk. The premature employment of concentrated alcoholic drinks, strong tea or coffee, must be warned against. Even with bouillon, which holds such a high place in dietetics, the writer has observed unfavorable excitement of the heart, annoying even to the patient himself when administered in concentrated form or at too short intervals. The voraciousness which comes on after a few days is naturally not to be yielded to, and the amount and kind of food must be limited. The frequent administration of small quantities is to be preferred to less frequent larger meals. The transition from liquid diet to ordinary food is accomplished gradually. At first we add to the milk, rice, grits, and mondamin, then lightly baked articles like roasted zwieback and biscuits; eggs boiled soft or hard and finely divided; later, fat in the form of butter or with vegetables like asparagus, spinach, and cauliflower. Of meats we may give first ham, white meat, and game, though at the beginning cut up small in soup.

Massage plays but a very slight rôle in treatment, and should be avoided till the recovery of considerable strength.

Remedial Treatment.—Medicaments are generally indispensable; for instance, anorexia or dyspepsia may be due to a diminution in the gastric juice (see above), and call for the administration of hydrochloric acid. Yet when associated symptoms like neuralgia or general nervous excitement necessitate the employment of suitable drugs, the susceptibility of the anemic organism must not be forgotten, and the doses made correspondingly small.

The rôle played by the *administration of iron* is not so great in acute anemia as in other anemic conditions; nevertheless, since this important question is here touched on for the the first time, the opportunity is taken of showing its present position.

The statement is not extravagant that there is a unanimity among physicians in regard to scarcely any other question such as that in regard to the effectiveness of iron in many anemic conditions. In anemia iron is, moreover, capable of producing its effect when no other therapeutic procedures are used. This is shown by hundreds of observations made by practical physicians for generations, and it has been again and again demonstrated by careful investigation in hospitals. In many of these instances every effort was made to remove all possible sources of error; for instance, the improvement was determined by accurate estimation of the increase in blood-corpuscles and hemoglobin; further by comparisons of the results in patients treated with iron and in those treated by other methods; and patients were even treated for a time without iron, and it was shown that the rapid improvement first set in with its administration (v. Ziemssen, Graeber, Hale White, Stockman, XXII. Congress of Internal Medicine, Nothnagel).

Extensively as iron therapy has been practised by physicians, physiologic and pharmacologic investigations have brought forward but few facts indicating its manner of action. The numerous investigations of the last ten years were stimulated by Bunge, who disputed every effect of iron, and claimed that all the results of clinicians were due to suggestion. It is impossible to go into detail in regard to the different phases of this investigation, and the writer therefore refers to the complete monograph devoted to this subject by Quincke in 1895.

Quincke's eminently successful monumental treatise, by putting the question on a new basis, has determined the direction of the work of late years. This period furnished the investigations of Macallum, Woltering, Kunkel, W. S. Hall, Gaule, Hochhaus and Quincke, and Hofmann, to which we owe the positive proof of the fact disputed by

Bunge, that iron in remedial doses, in both inorganic and organic form, is absorbed from the intestine. We know now that in man (Hofmann) as well as in experimental animals—rats, mice, rabbits, guinea-pigs—iron is absorbed particularly from the duodenum, but also in slight amounts from the jejunum and stomach (Hari). We know further that the absorbed iron enters the circulation by way of the lymph-tract, and is rapidly stored in great part in the spleen; a smaller portion being taken up by the liver-cells and the bone-marrow. These investigations, moreover, agree in showing that the iron is excreted especially by the colon, in smaller amounts by the rectum, and in insignificant quantities by the kidneys. This slight elimination by the urine explains why the occurrence of absorption was denied for such a long time.

Further than this investigation has not advanced, and we can not deny that our knowledge of absorption and elimination teaches us very little in regard to the mode of assimilation of the iron and of the elaboration of the hemoglobin. It is not very probable that the iron stored in the spleen and liver is directly employed in the formation of hemoglobin; on the contrary, the assumption, first suggested by v. Noorden, seems much more plausible, namely, that the iron exercises a direct irritative action on the function of the blood-making organs.

In later communications (see Häusermann) Bunge acknowledges the absorption of inorganic and organic iron preparations from the intestine, but insists, on the ground of animal experimentation, that iron has not a curative influence in anemic conditions. He contends that only the iron contained in the food is capable of increasing the hemoglobin of the blood. The Bunge-Häusermann experiments were done particularly on animals made anemic by the exclusive administration of nourishment poor in iron (milk and rice). Having been brought into an anemic condition, the animals received, in addition to the nourishment poor in iron, iron in medicinal form, yet the anemia improved but slightly. A mixed nourishment with a normal amount of iron, on the contrary, did away with the impoverishment in hemoglobin in a short time. Bunge had the same results in animals made anemic by repeated venesections.

These animal experiments can be regarded only as a proof of the inefficiency of iron in those rare forms of anemia which have a similar pathogenesis. That there are certain anemic conditions in which iron is useless—*e. g.*, progressive pernicious anemia—has been recognized by clinicians of every age. Bunge's experiments, therefore, signify but little in the greater number of anemic conditions, since, according to the majority of clinical observations, especially those on chlorosis, they

are inapplicable. Chlorosis can only exceptionally be referred to an insufficient amount of iron in the nourishment, nor can its condition be improved by selected food rich in iron, while the administration of iron in medicinal form quickly produces complete recovery without attention to the nourishment.

From these investigations the practical requirement is obvious that the different forms of anemia should be differentiated from one another in order that the conditions in which iron therapy is useless and is to be replaced by proper diet, be separated from those in which only the medicinal administration of iron is capable of producing a regeneration of the hemoglobin with or without change in diet.

Acute post-hemorrhagic anemia undoubtedly belongs to those conditions in which a mixed diet, especially of vegetables rich in iron, eggs, and meat, quickly produces a regeneration of the blood. Still, Eger, who made special experiments on animals, claims that the addition of medicinal iron to nourishment rich in iron hastens the improvement. It is, therefore, well since iron can not do harm when rationally administered unless an absolute idiosyncrasy exists, to hasten the cure by its administration in those cases of acute post-hemorrhagic anemia in which the restitution of the hemoglobin appears retarded.

The kind of preparation and the amount administered is of the greatest importance for the success of the therapy. Attention has recently been diverted from the innumerable new complicated organic preparations of iron continually being advocated to the remarkable results obtained by the older physicians with the inorganic preparations, especially ferrum reductum, ferrum carbonicum, etc. Still it must be confessed that among the new preparations there are a number which, in contrast to the old, irritate the stomach and intestine but little, and are agreeable in taste. There are no differences between the two classes as to the mode and extent of the eventual effect, since the majority of "organic" combinations of iron (albuminates, peptonates) are oxidized in the intestine, and are then under the same conditions, as far as absorption is concerned, as the inorganic preparations. Only a few highly constituted combinations, like hemoglobin itself, or substances allied to it, like *ferratin*, *carniferrin*, and others, retain the iron molecule in the intestine and seem to be especially easily absorbed (Quincke).

It is impossible for a physician to possess a personal knowledge of all the numerous preparations on the market. It would scarcely be justifiable, therefore, to insist on those which the writer has employed with success. Still he would like to recall the fact that the old remedies of the pharmacopeia (pilulæ Blaudii, tinctura Bestucheffi, etc.) are

undoubtedly capable of exercising very favorable effects. Modern combinations seem to avoid their evil effects, yet it must be remembered that to administer sufficient iron, certain of them must be given in doses that are just as harmful to the stomach and intestine, and much more expensive.

As a necessary requirement even the older clinicians insisted that the metal should not be administered in too small doses. At the present day about 0.1 gm. of metallic iron is generally considered as the proper daily dose. Quincke and v. Noorden showed in a detailed table what quantity of the different organic and inorganic preparations contained 0.1 gm. of iron. Among the highly constituted compounds, carniferrin and ferratin occupy the first place, 0.33 gm. of the first, 1.54 gm. of the second containing 0.1 gm. of iron. The same amount is contained in:

0.10	gm.	of ferr. reduct.,
0.16	"	of ferr. sulph.,
2.80	"	of tct. ferr. chlor.,
7.00	"	of tct. ferr. pomata,
25.00	"	of liq. ferr. albuminat. (Phar. Germ.),
3–4	"	of pilul. ferr. aloët.,
5	"	of pilul. Blaudii.

On account of the fact that the internal administration of iron frequently produces gastric disturbances, in the shape of pain, tenderness, loss of appetite, and nausea, the attempt has been made (Glaevecke) to introduce the remedy subcutaneously. The preparation employed was ferrum citricum oxydatum. The injection was made into the buttocks or the thick musculature of the back, and produced only a slight burning pain and a tenderness at the site of injection, lasting twenty-four hours. According to the reports of the author and several other clinicians, the results were at least equivalent to those observed after administration by the stomach. Still this method has not become common, very probably because there are sufficient preparations at our disposal capable of being administered without evil effects to the most sensitive individual. Moreover, according to Lewin, gastric disturbances occur even on subcutaneous administration. These undesirable effects are best avoided by administering the iron, no matter what its form, a short time after meals, never on an empty stomach.

SIMPLE CHRONIC ANEMIA.

With the exception of chlorosis and Biermer's anemia, all chronic anemias are only accompanying symptoms of some other pathologic condition, and are considered therefore under the general head of Symptomatic Anemias. This classification corresponds only partially with that which subdivides certain anemic conditions, the result of diseases of various organs or of the general constitution, under the broad designation secondary anemias. For in a certain sense acute post-hemorrhagic as well as the severe bothriocephalus anemia, and possibly also chlorosis, should be termed secondary diseases; though as a matter of fact the anemia in these cases is so pronounced and shows such a specific individuality that it can no longer be regarded as a symptom of the hemorrhage, of the helminthiasis, etc., but must be considered an independent disease.

[Floyd and Gies[1] described a case of severe simple anemia in a girl of nineteen. The blood count showed 750,000 red blood-corpuscles; 3300 white blood-corpuscles, 12 per cent. of hemoglobin. After fifteen months treatment, the blood recovered normal characters.

In the same connection certain severe anemias in which hypoplasia of the marrow has been discovered may be alluded to. Ehrlich himself first described such a case in a woman aged twenty-one years, in which extensive hemorrhages into the tissues and from the mucous membranes were the dominating clinical manifestations. The red corpuscles were reduced to 213,300 per c.mm., but no nucleated red corpuscles could be found. The leukocytes numbered only 200 per c.mm., of which 80 per cent. were leukocytes, 6 per cent. large mononuclears, and 14 per cent. polymorphonuclear neutrophiles. At autopsy the marrow was found yellow, having therefore failed to respond to the demand for increased function. Similar cases have been observed by others. In minor grades this condition of aplastic anemia is doubtless not uncommon.

Robert Hutchinson,[2] in his lectures on anemia of childhood, refers to a condition of interest here. Leaving out of consideration cases of malnutrition, wasting diseases, etc., the author believes there is a residuum of cases in which anemia can not be accounted for, and he reports briefly the features of 4 such cases. The health of the mother is naturally inquired into, but in these and similar cases he has not found any connection between these and the anemic state of the children. He notes the fact that the blood-making function is independent in mother

[1] *New York Med. Rec.*, April 27, 1901. [2] *Lancet*, May 7-14, 1904.

and child. In 2 of the cases reported, the mother had volunteered the statement that the appearance of the anemia had been preceded by severe jaundice, and the author thinks there may have been an unusual amount of blood destruction for which the blood-making organs could not compensate. The prolonged use of iron in these cases of congenital anemia does not correct the condition, and he believes that there is a congenital deficiency in bone-marrow. He refers to the case of Muir,[1] in which such deficiency developed in a boy of fourteen.—ED.].

In the introduction to this part of the book this general statement of the origin of anemia is given: An anemia is the result of a disproportion between blood formation and blood consumption. In case decrease of the first or increase of the second is responsible, the writers, with Immermann, speak respectively of a "hypoplastic" or a "consumptive" anemia. If both factors act together, a "complex" anemia is spoken of.

Apart from post-hemorrhagic anemia, which may be regarded as the purest type of the consumptive form, only complex anemias are seen in practice, even though in one case the increased consumption, in another the decreased blood-formation exercises the greatest influence. In fact, in the majority of cases the pathologic processes are so varied and to a great extent so obscure that it is impossible in individual cases to express an absolute opinion as to the consumptive or hypoplastic nature of the anemia, especially since the different pathogenesis lends no characteristics to the disease-picture. Hayem, therefore, properly insists that it is impossible to classify the chronic anemias from the alterations in the blood-picture, and claims that the differences are only in degree, and that every cause which can produce anemia may produce either a mild or severe form, so that from the severity of the disease no conclusion can be drawn as to its etiology.

In a comprehensive discussion of the simple chronic anemias, therefore, it appears advisable to subdivide the special etiologic factors, but to discuss the symptomatology of the whole group together, taking up only special peculiarities of the blood or of the clinical picture separately.

Simple chronic anemia occurs:

α, after frequently repeated hemorrhages;

β, on continued undernourishment and as the effect of other factors contrary to the requirements of hygiene;

γ, in association with and as the result of other diseases;

δ, after acute and chronic intoxications.

[1] *Brit. Med. Jour.*, Sept. 29, 1900.

THE ORIGIN OF SIMPLE CHRONIC ANEMIA.

Subacute and Chronic Post-hemorrhagic Anemia.—In the discussion of acute anemia we saw that even small losses of blood (50 c.c.) produced evident changes in the blood of adults, though a healthy organism readily returned to normal. Yet if in a comparatively short space of time even these small hemorrhages were frequently repeated, the power of regeneration often proved insufficient and a chronic anemic condition developed as a consequence. Such chronic hemorrhages are produced by numerous causes.

Apart from rare causes we may mention: 1, Epistaxis, which as a rule is produced by some general disturbance of the circulation, hemophilia, ulceration of the mucous membrane, etc.; 2, pulmonary hemorrhages (in phthisical patients) which are differentiated from others of this group by their intensity; 3, hemorrhages within the intestinal tract produeed by parasites (Ankylostomum duodenale), ulcus ventriculi et duodeni, malignant tumors, hemorrhoids[1]; 4, in women hemorrhages from the genitalia produced by abnormal increase of menstruation or inflammatory processes or tumors, especially myomata; 5, vesical hemorrhage from cystitis and tumors; 6, different forms of the general hemorrhagic diathesis.

In only a few cases of this group can the actual effect of the hemorrhage be observed, since in the majority the picture is confused by complications like fever, lack of nourishment, and intoxications. Still certain conclusions have been reached from animal experiments.

The effect of repeated hemorrhages on the organism is obviously decided by two factors: 1, The size of the individual hemorrhages; and 2, the rapidity with which they follow one another.

From the writer's experience in regard to the regeneration of the blood after a single hemorrhage, it is evident that very great losses may be entirely replaced in a reasonably short time. Moreover, Quincke has shown that almost double the entire amount of blood may be gradually withdrawn from dogs in the course of four or five months and be completely restored. The necessary requirement for this compensation is the allowing of a sufficient interval between hemorrhages for a complete regeneration. In man exact statistics are wanting, yet repeated clinical experience, especially from olden times, when venesection was in vogue, would seem to indicate that even repeated great losses of blood leave behind no chronic alterations when the intervals between the individual hemorrhages are long.

[1] It may be mentioned here that several writers—*e. g.*, Dunin—regard chlorosis as a result of repeated small losses of blood within the intestinal tract.

Other effects naturally come into play when a second loss of blood occurs before complete regeneration. Under these circumstances considerably smaller losses than Quincke found necessary in his experiments on animals can produce severe chronic, even irreparable, injury to the organism.

How great an amount of blood a man can lose by frequently repeated hemorrhages in a comparatively short time, can naturally not be determined even approximately. Alexandrew, a Russian physician, who was affected with phthisis and frequently suffered from hemoptysis, measured every time the amount of blood lost, and claims he lost in six and a half months about 20 kg. blood—*i. e.*, with a body weight of 65 kg., about four times the entire amount of blood. Yet, according to his own report, he recuperated fully. That continued insignificant losses of blood following one another at not very great intervals must lead to a chronic anemic condition, is evident from the general effect of hemorrhage, which is discussed under Acute Anemia. As long as the regeneration continues to be interrupted, so long will the blood be unable to attain its full value in individual constituents. If then the hemorrhage eventually ceases, the restitution proceeds much more slowly than after a similarly severe acute anemia. Thus it has been shown in experiments on animals that the period required for complete restoration is greater the more frequently the hemorrhage is repeated. Laache compared corresponding clinical observations with one another. He found, for instance, in a case of acute post-hemorrhagic anemia that the number of blood-corpuscles increased within two months from 1,600,000 to normal, while an increase from 2,500,000 to normal in a case of hemorrhoids in which anemia was produced by frequent hemorrhages occurring over years, required eight months, although no new hemorrhages occurred after the beginning of observation.

Morever, beyond certain limits, the organism is incapable of compensating for alterations produced by repeated hemorrhages; though individual differences in this regard are marked.

If the strength of the body is broken down, a chronic anemia develops which can be differentiated from the simple chronic anemias of different origin by no special characteristics, and its symptoms, therefore, will be described later in common with those of the whole group.

The Origin of Simple Chronic Anemia Through Unfavorable Hygienic Conditions.—The group of post-hemorrhagic anemias, the etiology and pathogenesis of which are known from clinical observation and experiment, is followed by another very important group referable to the protracted action of unfavorable hygienic

conditions, though the particular causative factors are not very clear. Nevertheless, from a careful study of the anamneses in these cases it appears obvious that not one factor alone, but several acting together, produce the alteration in the blood, since it is scarcely ever possible to point to the violation of only one hygienic condition. The most frequent examples are found among the laboring classes in the large cities, when the anemia may be regarded as the result of all the harmful influences with which the struggle for existence is associated: An insufficient amount and poor quality of food; dwellings which with their want of light and pure air contradict all hygienic requirements; excessive bodily efforts, insufficient recreation, and, in addition to these physical ills, mental care and trouble. The protracted action of this multiplication of ills leads in predisposed individuals to all sorts of organic disease, and in the strongest may undermine the resisting power, with the production of a chronic anemia. Though these relations are known not only to every physician, but also to every intelligent person, and seem a matter of course, an exact scientific analysis of them has not been successful, in fact, has scarcely been attempted. The chief reason for this lies in the fact that such patients manifest only a simple anemia without organic disease, and usually fail to come under clinical observation, either because they do not recognize their diseased condition or because they attribute to it too little significance.

Nevertheless the fact has become so important to the physician and hygienist that numerous experimental studies have been devoted to the influence of the individual hygienic factors on the composition of the blood. The writer must insist, however, that we should be still very far from a satisfactory explanation of the action of the combined factors even after we succeeded in obtaining positive knowledge in regard to the effect of one.

The **influence of insufficient nourishment** on the composition of the blood has been studied comparatively more than any other factor on account of the great interest centering in this question from the standpoint of physiology and pathology.

Numerous prominent investigators, among whom we may mention especially Heidenhain, Panum, and C. Voit, have demonstrated in both animals and man the influence of insufficient and poor nourishment. What hematology has learned from these experiments, we shall detail in the following:

The first experiments attracting our attention are those which show how the human or animal organism reacts on the entire withdrawal of nourishment. Considerable knowledge has been gained in this direction

from the so-called "fasting artists," who voluntarily deprive themselves of nourishment for a long time while drinking copiously of water. Consequently, omitting a few questions, we are not obliged to apply the results of animal experimentation to man, a procedure which, particularly in hematology, may give rise to gross errors.

The writer will begin with the investigations made by Senator and F. Müller on the fasting artists, Cetti and Breithaupt, while they were absolutely deprived of nourishment, though taking as much water as they wished. Cetti's fasting period lasted ten days, during which the body weight sank from 57 to 50 kg. The hematologic investigations on him were limited to the determination of the relative amount of hemoglobin and the counting of the white and red corpuscles. The number of red blood-corpuscles per c.cm. was about 1,000,000 higher at the termination of the experiment than at the beginning. The number of leukocytes decreased from 12,000 to 4200, the percentage of hemoglobin from 115 to 85–90 per cent. In the case of Breithaupt, who fasted only six days and decreased in weight 3.5 kg., the number of red blood-corpuscles remained practically unchanged, the number of leukocytes sank to 6500, and the percentage of hemoglobin increased from 107 to 130 per cent.

Since these results of Senator and Müller are in complete accord with numerous previous experiments on animals and other observations on fasting individuals, they are sufficient to show that the sudden absolute withdrawal of food is not capable of producing oligocythemia or oligochromemia. Still in these cases considerable influence is probably exercised by the circumstance that the persons in question enjoyed every hygienic advantage, and, since they undertook the experiments voluntarily, were free from every mental worry.

Moreover, the observations on man require animal experimentation to complete them, since only in this way can we obtain a knowledge of the behavior of the whole amount of blood in such experiments. The entire agreement of the experiments on animals made by Heidenhain, Panum, and Voit shows evidently that in fasting animals the blood experiences an absolute loss almost exactly proportional to that of the whole body weight. Accordingly the percentage relation of the blood to the whole body weight remains undisturbed. For instance, the amount of blood in Voit's normal control dog amounted to 8.5 per cent. of the weight of the entrails and muscles, in the fasting dog to 8.8 per cent.; the blood of the latter contained 21.75 per cent. solid constituents, of the former 18.11 per cent. Further, the relative proportion of the important constituents of the blood to one another was not

markedly altered; according to Panum, only the dried substance of the serum (both the albumin and its salts) experienced a decrease.

Although from these experiments it would appear that a pretty considerable absolute diminution of the amount of blood could be brought about by inanition, it would not be proper to speak of an oligemia, since the animal in question possesses exactly as much blood as a normal healthy animal of similar body weight.

From exact experiments on man and animals, therefore, the conclusion can be drawn that sudden absolute withdrawal of nourishment is not capable of producing an anemia.

By no means so definite an answer can be given concerning the influence exercised by subacute or chronic lack of nourishment on the composition of the blood. In contrast to acute inanition, which is practically of only theoretic interest, the investigation of the effects of a periodic or long-continued lack of sufficient nourishment constitutes one of the most important questions in practical hygiene and clinical medicine. To indicate even the general lines of such an investigation would carry us far beyond the scope of this work. We can only give, therefore, the facts that hematology has acquired from these investigations.

The idea is general that insufficient nourishment produces an impoverishment of the blood, and it has taken deeper root on account of the fact that poorly nourished individuals are almost invariably very pale. Moreover, an *a priori* connection between lack of nourishment and anemia is quite plausible. In Immermann's sense this form of anemia would be to a certain extent the opposite of the acute post-hemorrhagic, and might be designated the purest type of "hypoplastic" anemia.

Further observations on man and animals, however, forced the rejection of this idea.

Sahli first, after him Laache, Oppenheimer, and others, demonstrated that individuals with very pale skin and mucous membranes frequently showed a normal percentage of hemoglobin and a normal number of corpuscles. This fact has been repeatedly confirmed, especially in patients considerably emaciated by some fundamental disease—*e. g.*, tuberculosis.

[It has been found that the pallor of certain diseased conditions, such as arteriosclerosis, nervous disorders, and the spurious anemia of new-comers in tropical countries, is not accompanied by any reduction in the number of corpuscles or the amount of hemoglobin. The phenomenon is doubtless due to vasomotor conditions, and the term angiospastic pseudo-anemia has been suggested.—ED.]

These observations alone are sufficient to prove that the relation

between nourishment and the condition of the blood is by no means so close as we might be inclined to assume.

This question was taken up by the physiologists long before the clinicians. They taught that it was not so much a lack of nourishment as a deficient quality of nourishment which exercised an unfavorable influence on the composition of the blood. Verdeil demonstrated in 1849 that dogs fed with bread showed a considerable less quantity of iron in the blood ash than when fed on a rich meat diet. Later Voit and his pupils (see Ssubottin) demonstrated the general principle that the hemoglobin percentage of the blood fluctuates according to the amount of albumin in the food.

These investigations were recently taken up by v. Höslin. He determined first, in experiments continued over months, that a chronic even high-grade lack of nourishment *per se*, though it is capable of producing an extraordinary loss of weight, is not capable of reducing the quality of the blood.

He took two dogs of the same litter and of pure blood, and fed one (primary weight 3.2 kg.) from the beginning with only one-third the amount of nourishment of the other (primary weight 3.1 kg.). On the fifty-sixth day the latter weighed 11.6 kg. and showed 10.2 per cent. hemoglobin; the other 5.5 kg. and 11.2 per cent. hemoglobin. After four months the figures were:

		Kg.	Bb.	Red blood-corpuscles.
	I.	23.4	14.9	6.62 millions
	II.	8.5	16.0	7.97 "
After one and one-half years . . .	I.	30.3	17.6	8.3 "
	II.	9.5	15.5	7.3 "

It is clear that experiments in this direction can not be done on man. Those done by Grawitz on himself and several other healthy individuals were naturally of very short duration, so that the transitory lack of nourishment did not even lead to a decrease in weight.

v. Hösslin further studied the influence of qualitatively defective nourishment, and demonstrated by animal experiments that only a **diminution of the iron in the nourishment,** not of the albumin, as previously believed, was capable of producing alterations in the composition of the blood, especially an impoverishment of hemoglobin. The lively discussion of late years on iron therapy has brought out a number of investigations similar to this (Bunge, Kunkel, and others), and in confirmation of Hösslin's results it has been frequently shown that anemias, even of severe degree, could be produced by nourishment which was devoid of iron—*e. g.*, by an exclusive milk diet continued beyond the time of physiologic lactation.

Häusermann reports the only single analogous case in man. He had the opportunity of observing an eighteen-year old industrial pupil who had never eaten anything else than milk. Now and again he had made the attempt to eat bread and fruit, but could never become accustomed to them; for meat, eggs, butter, cheese, and vegetables he had an unconquerable distaste. His general constitution was that of pronounced anemia: pale-yellowish color, cold feet and hands, easily fatigued, ready excitability of pulse, etc. The number of red blood-corpuscles amounted to 5,000,000, the percentage of hemoglobin to 60 per cent. (Gowers).

Undoubtedly then the greater number of "anemias from inanition" are to be explained by the want of those nutritive substances from which the body derives most of its iron, in other words, especially meat. Since this is relatively the dearest article of diet, poor people often obtain it only in insufficient amounts or even not at all. Moreover, the same is true in the cities in regard to the vegetables containing the most iron, like spinach, asparagus, and fruit. Deprivation of these articles seems to constitute one of the most important causes of anemia in the lower classes.

A second factor to which is commonly attributed a large influence on the proper composition of the blood, is **light**. In fact, hemoglobin has often been compared with chlorophyll on the theory as the latter is elaborated only in the presence of light, the formation of hemoglobin also requires it. One argument for this view was found in the fact that the inhabitants of dark dwellings are frequently pale and anemic. Nevertheless the investigations of recent years have shown that this idea is groundless, and directly contradicts exact observation. Schoenenberger, in a complete monograph, has stated our knowledge of the physiologic effect of light, paying particular attention to the effect of the removal of light on the blood. He presents two observations which show better than any laboratory experiment that even a long-continued absence of light, when the other vital conditions are not unfavorable, produces no bad effects on the organism. He obtained reports from a large number of veterinary surgeons as to the health of horses which for ten to twenty-four years uninterruptedly worked in mine-pits without exposure to one ray of sunlight. According to these reports, the horses remained in excellent health, and no disease was ever observed which could be referred to the want of light. He further mentions the report of the physician (Dr. Blessing) on Nansen's North Pole Expedition, which expressly states that the blood examinations made during three long polar nights of one hundred and forty to one hundred and fifty days each showed no anemia or other deterioration. This would go to prove that in the case of other polar explorers who

manifested a greenish-yellow color of the skin and other disturbances of health under the influence of the polar night, the blame should be laid not on the want of light, but on other unhygienic conditions.

After these two series of observations, which, as far as the deprivation of light is concerned, are extreme in their duration and intensity, animal experiment seems superfluous. The writer, therefore, mentions only in brief Schoenenberger's experiments, in which he left several rabbits thirty to forty days in absolute darkness. He was then able to demonstrate the surprising fact that the entire blood showed during this time a progressive though moderate increase in cells and solid constituents. A microscopic examination of the blood showed no noticeable deviation from the normal. Accordingly, we must conclude that an absence of light is not concerned in the origin of anemia.

An unfavorable influence on health is undoubtedly exercised by the **bad air** in the dwellings of the poor in city and country. We consider the air bad when contaminated by gaseous constituents which offend the sense of smell or actually irritate the respiratory passages. Omitting contamination produced by manufacturing industries, the most important is that arising from decomposition of the waste products of the human economy. Mention may be made especially of hydrogen sulphid, ammonia, and volatile fatty acids, which, according to Flügge, are often mixed with the air in such small amounts that they can not be demonstrated chemically, though they may torment the sensitive sense of smell. The explanation of the evil effects of bad air on the health is likewise not satisfactory. True, in bad air a sensation of nausea is frequently experienced, and the respiration becomes superficial in the involuntary endeavor to limit to the utmost the entrance of the noxious vapor. Yet these sensations are quickly blunted, and even very sensitive persons soon fail to notice a bad odor to which they are persistently exposed. The respiration also becomes normal. Still, it can not be said that the continued contamination of the air by noxious gases, even when very slight, is incapable of influencing the composition of the blood.

Further than this the writer can not go. Consequently at the close of this section he must repeat the indubitable statement that a continuous or serious violation of hygiene produces in numerous individuals a chronic condition of anemia, though he is unable to define more accurately its mode of origin, except that the greatest significance is attributable to insufficient nourishment.

Anemia as an Associated Symptom and Sequela of Other Diseases.—On account of the close metabolic relations which

the blood bears to all the organs of the body there is scarcely a pathologic process of any extent without the blood showing some manifestation. Still the anticipation has not been fulfilled that definite changes in the composition of the blood would be found corresponding to definite diseases, thereby aiding both diagnosis and prognosis; though the investigations of acute and chronic diseases have brought forth so many positive results in this regard that it is now the duty of the clinician to develop this material possibly by means of finer methods in order that it may take on its proper practical significance.

Among the alterations which the blood experiences in conditions apart from specific hematologic diseases, only a small portion can be described as anemic in character; for while many conditions produce alterations in certain of the chemic and morphologic constituents of the blood, the amount of hemoglobin usually remains normal. Still every disease can produce anemia through secondary influences, though the writer intends to discuss chiefly certain definite pathologic conditions in which anemia develops more or less regularly or to a marked degree.

When one considers in a general way how diseases of various organs may produce a deterioration of the blood, attention is at once attracted by the causes of anemia discussed in the two preceding sections. In the first place, apart from a very few isolated conditions, almost all diseases are associated with a diminution in the amount of nourishment. This belongs sometimes to the nature of the disease itself—*e. g.*, in diseases of the digestive tract—or is the result of the disturbance of appetite produced by the rest in bed, fever, etc. The effect of this relative inanition is naturally increased when combined with other influences.

Moreover, a small number of diseases are associated with more or less severe losses of blood (compare p. 187), with the result of a posthemorrhagic anemia, which is increased by the blood lesions of other origin.

When the anemic condition arises through loss of blood-tissue itself, the connection between cause and effect is very apparent. Still, besides this group there are other anemias which are the result of the pathologic loss of other valuable tissues. Among these may be mentioned, first, subacute or chronic processes in which a highly organized material rich in cells is withdrawn in large quantities from the organism; for instance, long-continued **suppuration.** In this, important constituents of the body are lost, which require for their elaboration a considerable expenditure of strength. It needs no proof to show that in the economy of the organism defects must arise when such a highly valuable material

is produced in large quantities and is lost without performing its function. Moreover, an excessive loss of highly important chemic substances containing no cells—*e. g.*, albumin, in albuminuria or exudate formation—must produce similar results.

Still in this case the connection between the cause and the effect is not so clear. Experimental investigations, from which we were able to derive so much information in the discussion of the post-hemorrhagic condition, are almost entirely wanting. In addition, the question in this case is much more complicated, since the effect of the loss of cell-substance is only one effect, and probably a comparatively small effect, of the general action of the suppurative process. Further, when we compare the large amount of cell material eventually lost to the body, this seems to exceed greatly the loss of substance in acute, subacute, and chronic hemorrhages. Though in a post-hemorrhagic anemia the loss of red blood-corpuscles is naturally the most important factor in the origin of the anemia, a comparison is still possible, since the white cells of the pus are, on account of their high nuclein content, of great histologic value. Moreover, to this direct loss of the body constituents is added an extraordinary activity of the bone-marrow, which in long-continued suppuration is obliged to satisfy the increased demands. We can not refrain from the conjecture that on a long continuance of this condition the physiologic function of the bone-marrow (the new formation of blood) must suffer. A valuable support for this view is found in the observations of Roger and Josue. They examined histologically the bone-marrow after experimental staphylococcus infection, and found the fat considerably diminished and the cells proliferated, among the latter the granular neutrophiles, especially the mononuclear variety, predominating. The eosinophiles were relatively scanty in number. We recognize, therefore, in suppuration, apart from the effect of the fever and the bacterial toxins, which will be discussed later, two factors which hold a relation to the subsequent anemia, namely, the loss of highly valuable material and the overstimulation of the most important blood-making organ.

The effect of the mere loss of substance in suppuration on the production of the anemia can be seen in analogous processes, for instance, **spermatorrhea, lactorrhea,** and excessive losses of epithelium and mucus in catarrhs of the respiratory or digestive tract. The increased activity of the glandular secretion is analogous to the increased activity of the bone-marrow. In addition to the loss of material, therefore, a decrease in strength takes place, since the increased cell activity is in no way beneficial to the organism.

We must include with these conditions the loss of valuable chemic non-organized substances, especially albumin. The relations between **albuminuria** and the composition of the blood excited the investigative zeal of the older scientists, like Andral and Gavarret, Frerichs, Cohnheim and Lichtheim, and others, but in late years even more numerous researches have been undertaken, among which may be mentioned those of Hammerschlag, Dieballa, and Askanazy.

Dieballa averaged a large series of estimations in order to show the relation between the degree of the albuminuria and the hydremia. Yet as simple as the relation seems to be on first glance, it becomes more complex the deeper one goes into detail. The loss in albumin through the urine is in but few cases sufficiently large to make the metabolic balance negative. Moreover, the loss can readily be replaced by food. Nevertheless, in many such cases we see an undoubted anemia develop. So far, no satisfactory explanation has been made, so that many writers attribute the anemia to complications like loss of appetite, disturbances of digestion, etc., while others refer it to the toxic effects exercised by substances retained in the circulation on account of defective renal function.

Though the explanation of the origin of hydremia from albuminuria is difficult, the hydremia itself can not be doubted. Moreover, that the hydremia may prove directly injurious to the red blood-corpuscles, and so lead to a true anemia in the sense of an absolute diminution of hemoglobin, has been previously shown in several places.

A symptom to which the greatest importance is generally attributed in the origin of anemic conditions is **fever.** Daily experience demonstrates that a whole series of acute and chronic febrile conditions produce the clinical syndrome of anemia. Although the apparent anemia has not rarely been a delusion produced by vasomotor influences, the special examination of the blood has not infrequently determined a decrease in hemoglobin. Moreover, though the hemoglobin estimations are not absolute, and marked transitory differences in quantity may be produced by the taking up or the giving off of water, a series of facts can be brought forward to show an actual decrease of hemoglobin in fever. Among these there is, first, hydrobilirubinuria. Viglezio was the first to advocate the view that the amount of urobilin is a criterion of the destruction of the red blood-corpuscles by infectious and toxic agents. The icterus and increased hydrobilirubin excretion in the urine observed in connection with tuberculin reactions is likewise attributed by Hoppe-Seyler to a destructive effect exercised by large doses of tuberculin on the blood coloring-matter.

Though we have absolutely determined that the blood does deteriorate under the influence of fever, it is not clear what factor plays the decisive rôle. According to present day views, this question must be treated similarly to the investigation of the relations between febrile diseases and albuminous decomposition. In this regard, as is well known, numerous reliable investigators have shown that **elevation of temperature** *per se* produces only a slight part of the increase in tissue breakdown. In an analogous way an attempt has been made to study, by means of artificial hyperthermia, the factor in the fever which plays the chief rôle in the deterioration of the blood. According to the observations of Breitenstein, A. Löwy, and others, artificial hyperthermia appears to have no influence on the composition of the blood, and causes only variations in its distribution through vasomotor action. Ziegler and Werhowsky alone report in animals, which they kept for different lengths of time (two to twenty-nine days) at an incubator temperature, an enormous increase of hemosiderin in the bone-marrow and spleen as a sign of increased destruction of hemoglobin.

Still, one must realize that artificial heating of an animal by elevation of the external temperature is by no means identical with fever, and that the results obtained by such methods are not to be considered as contributing much to the knowledge of febrile conditions. Only by the aid of **toxic substances** can fever be produced experimentally in any way analogous to the natural pathologic process. With this in view considerable zeal has been expended in regard to the effects of the proteins and the metabolic products of bacteria on the animal and human organism. The majority of facts in this direction have been collected from experiments with Koch's tuberculin; and these investigations have proved very instructive for hematology.

The influence of bacterial toxins on the blood apart from the direct production of anemia is observed in alterations in the number of leukocytes, in increase or diminution of the watery constituents, or in modifications of the distribution of the blood. The relation of all these factors to anemia has been discussed in other sections.

The writer can do no more than mention here the important and interesting observations on the chemotactic effects of bacterial toxins, namely, hyperleukocytosis and hypoleukocytosis, and must refer for further details to Part I. of this volume. Moreover, he can only touch on the investigations which demonstrate an increase in the lymph circulation from the action of bacterial toxins, for instance, tuberculin and pyocyaneus toxin (Gärtner and Roemer); and further, the experiments of Bouchard, Charran, and Gley, which show that bacterial extracts—

e. g., of the pyocyaneus—contain certain substances capable of diminishing the excitability of the vasodilator centers and others capable of acting in the opposite way.

Investigations on the production of anemia by the action of bacterial toxins which would interest us here are still scanty. Fischl and Adler observed a case of severe anemia in which shortly before death a streptococcus was found in the blood. From the general behavior of the case the investigators drew the conclusion that the entire condition, which lasted about three months, was a septicemia characterized principally by the severe anemia. They tested, therefore, the toxic properties of the isolated coccus by intravenous injection into rabbits of sterilized bouillon cultures which contained the toxin of the cell-bodies as well as the metabolic products. The result was a rapid diminution in the number of blood-corpuscles within a few days (from 6,000,000 to 1,300,000 in seven days). Similar observations were made by Finkelstein in a case of hemorrhagic diathesis in a newborn child. In this case shortly before death an extraordinarily small number of red blood-discs were found, some of which were very pale and stained poorly, others were completely washed-out shadows. After staining with carbol-fuchsin, diplostreptococci, which proved on culture to be true streptococci, were found both free in the blood, and especially in the decolorized blood-discs. E. Grawitz observed a case of very acute streptococcus infection in which the destructive effect of the streptococcus toxin produced an enormous erythrocytolysis, so that after the course of a few hours only 300,000 red blood-corpuscles were found in a previously healthy woman. Bianchi-Mariotti, with this end in view, tested the effect of typhoid, cholera, anthrax, and pyocyaneus bacteria, and found that the amount of hemoglobin invariably decreased after the injection of their metabolic products, and that this decrease seemed to hold a direct relation to the amount of the injected substance.

These observations are primarily of value only in explanation of the hemoglobinemic process, though from them it is possible to conclude that the bacterial toxins in much smaller doses may constitute the principal factor on account of their association with the fever, which has itself an anemic effect.

[Recent investigations in hemolysis have shown that a great variety of toxic products of bacteria and other organic poisons are capable of disorganizing the blood and causing severe grades of anemia.—ED.]

Turning to those diseases which experience shows lead especially frequently to anemic conditions, one is attracted first to the **diseases of the digestive organs.**

We may say that every disease of the digestive tract, when it is not entirely too slight, is associated with deterioration of the blood. Catarrhs and the different inflammations of the stomach and intestine, ulcus ventriculi and duodeni, chronic constipation, acute and chronic infectious diseases in connection with the digestive tract, tumors, nervous gastro-intestinal affections, and finally, even hemorrhoids, are frequently the cause of anemic conditions. Apart from the rarer complications of hemorrhage and suppuration, this effect is produced principally by disturbances of nutrition and by the elaboration of toxins in the gastro-intestinal canal.

The disturbances of nutrition may be partly caused by the loss of appetite, which decreases the amount of nourishment ingested. Still, in addition in many gastro-intestinal diseases, the ingested nourishment is by no means equivalent to the same in health, for, in the first place, the transformation necessary for resorption and assimilation is complete, because the secretion of the digestive juices is abnormal; and, in the second place, resorption itself is markedly influenced. Moreover, an increased peristalsis sometimes sets in which increases the disturbances of digestion and absorption. The result of these factors is a relative inanition, the significance of which, as far as the pathogenesis of anemia is concerned, has been previously discussed.

These disturbances are usually associated with toxic processes. They are the result of the decomposition of nutritive substances or possibly of the secretions from the intestinal mucous membrane. The investigations are yet too few to say with certainty whether a deterioration of the blood can be brought about by a defective excretion and consequent absorption of the normal products of decomposition, or whether the noxious substances are elaborated during abnormal decomposition of the ingesta. Vanni did some experimental work in this direction by producing an artificial coprostasis in dogs and rabbits. He found, when the fecal stasis was continued only a few days, a constant diminution of the number of blood-corpuscles, though almost no change in the amount of hemoglobin. From this Vanni drew the conclusion that the toxins absorbed on account of fecal stasis exercised a hemolytic effect.

Similar views are held by a large number of investigators who defend the intestinal origin of chlorosis. They consider that not only is the circulating blood modified in its composition, but blood formation itself is interfered with by this intestinal *auto-intoxication*. The arguments for this view are based principally on the undeniable effects of laxatives in certain cases of chlorosis, though on account of the fre-

quent failure of this method of treatment, they are, to say the least, very weak. On the whole, it may be said that there is as yet too little positive material on intestinal auto-intoxication from which to make a hypothesis of the origin of anemia.

(For the significance of the atrophic processes of the intestinal walls in the pathology of anemia, see the section on Progressive Pernicious Anemia.)

In addition to the gastro-intestinal diseases, there are others with which anemia, even severe anemias, are frequently associated. Among these may be mentioned **syphilis.** While ignoring for the present whatever etiologic rôle syphilis may play in Biermer's anemia, the writer must insist that in all its stages it is capable of producing ordinary anemia. Grassi and Laache and many others have accurately studied these relations. From their observations it appears that even the primary symptoms may be associated with a pure anemia, though, as a rule, the blood remains unaltered in this stage. Secondary syphilis shows a diminution in the number of blood-corpuscles and the percentage of hemoglobin much more frequently, and this condition continues as long as the syphilitic symptoms are active. Still, the severest forms of anemia are encountered in the tertiary stages of syphilis; in other words, in individuals who were infected a long time before. They are frequently so severe as to occasion confusion with Biermer's anemia, and in the section on Diagnosis the writer intends to devote special attention to them.

In a disease the etiology of which is not known, and which is almost completely closed to experimental investigation, we must trust to analogies with other diseases in order to explain its symptoms. Corresponding, therefore, to our knowledge of other infectious diseases, there is at present a general tendency to attribute the anemia of syphilis to a specific toxin.

The origin of the anemic condition in **malaria** is much more apparent. The direct destruction of enormous numbers of red blood-corpuscles by the specific parasites must, even in uncomplicated cases, lead to anemia, provided the infection is not recognized very early and properly treated or resists the therapy. Among the complications of malaria, blackwater fever especially produces anemia of the severest kind on account of the intense acute hemolysis. Further investigation may possibly show that the malarial plasmodia, in addition to their power of directly destroying the erythrocytes, produce toxic substances which are also capable of exercising an anemic effect.

A further large group of diseases in which we almost regularly find

more or less severe symptoms of anemia are **tumors.** In the discussion of the manner in which a tumor influences the composition of the blood, we must naturally omit all peculiarities and complications, for instance, a tumor may be so situated that it compresses an important organ—*e. g.*, the trachea or lungs—thereby producing disturbances of respiration which in turn lead to alterations of the blood. Further, every tumor of the bone-marrow of any considerable size must alter materially the composition of the blood, even though it is hematologically benign. Finally, we must leave out of consideration tumors like, for instance, those of the uterus associated with severe hemorrhages, and those which in their terminal stages exhaust the organism by ulceration and suppuration.

Working from this point of view, Bierfreund examined a large number of cases, and furnished a considerable amount of valuable material. His observations show that benign, uncomplicated tumors, even when they are characterized by rapid growth or considerable size, exercise no influence on the composition of the blood; further, that malignant tumors, even when not characterized by large size, special localization, or any complication (*e. g.*, sarcoma of the testicle or individual long bones, carcinoma of the breast, etc.), cause a reduction in the percentage of hemoglobin, which amounts on an average to about 15 per cent. (Fleischl). Moreover, when these tumors are of considerable size or rapid growth, even when not associated with functional disturbances or ulcerations, the oligochromemia is much more pronounced and the hemoglobin loss is almost double that of the previous category.

Further observations of Bierfreund's show other differences characteristic of benign and malignant tumors. He estimated the percentage of hemoglobin in cases of tumor previous to operation, and the diminution produced by the hemorrhage during the operation, and noted the period of time required for the return of the hemoglobin to its former percentage. He found that the regeneration of the blood after operations on benign tumors, even when the loss of blood was great, required no more time than an equally severe uncomplicated acute posthemorrhagic anemia, while in the case of malignant tumors the regeneration was considerably prolonged.

This difference between these two varieties of tumors is so striking that one is justified in assuming that the malignant tumors exercise a specific influence on the composition of the blood. A similar difference is found on the investigation of the metabolism of tumor cases, the malignant tumors differentiating themselves from the benign by an

increased excretion of nitrogen ; in other words, by an increase in albuminous decomposition (Fr. Müller, G. Klemperer).

While the etiology of tumors is obscure, we are forced to attribute the anemia associated with maligant tumors to specific toxins. It is likewise obvious that these are the cause of the marked increase in albuminous decomposition and of carcinomatous coma which manifests the classic picture of a true general intoxication, though the question still remains open whether the anemia is the result of increased destruction or is produced directly by the tumor toxin. Cases in which the tumor is small in size and the nutritive condition is very satisfactory, while the anemia is very advanced, are not rarely observed, and would seem to point to the latter. In later stages the injurious effects produced by the destruction of the corpuscles also come into play.

Grawitz endeavored to determine experimentally the effect of this toxin on the blood by making extracts of tumors and injecting them into rabbits. He found a considerable thinning of the blood, due to the taking up of water. Those substances which produce in experimental animals a lymphagogic effect on the blood, are in patients apparently excreted from the tumor in small amounts and cause an absorption of water which dilutes the blood. In addition to the relative diminution in hemoglobin thus produced, we have the direct anemic effect of the hydremia. From his experiments Grawitz was able to state that the injected extracts did not exercise a direct influence on the red blood-corpuscles or hemoglobin of the rabbit. Still, experiments of this sort can not be applied to human pathology on account of the immunity of experimental animals to cancer. Ehrlich's late investigations on the action of toxins, and his explanation of predisposition by the theory of the specific side chains of the cell-protoplasm, must warn us from considering the behavior of one species of animals as applicable to another.

Though with a better knowledge of the nature of malignant tumors the explanation for the associated anemia will probably become evident, the fact can not be doubted that an anemia may be the result of an uncomplicated tumor, and that the capability of producing a severe anemic condition is intrinsic to the tumor itself.

We come now to the discussion of another large group of parasitic diseases which frequently produce anemic conditions in man, and in which the origin of the anemia is to be attributed in the majority of cases to poisonous substances, namely, the different forms of **helminthiasis.** In the first part of this volume it was shown that helminthiasis almost always influences the morphologic composition of the

blood in the way of a marked eosinophilia (see Bückler). According to the conclusions expressed in another section, this eosinophilia demonstrates that the helminthes are not only locally irritant, but are also capable of exercising distant and general effects by the excretion of soluble absorbable substances which are taken up by the general circulation. Consequently, in lieu of a better explanation, these cases of worm anemia are referred to the action of toxins. Since Reyher, in 1886, first attributed to Bothriocephalus latus a toxic and specifically destructive effect on the red blood-corpuscles, many investigators have turned their attention to this subject. For a long time the "reflex theory" (reflex stimulation of the nervous centers) constituted the only explanation of the different disease symptoms; but now, corresponding to the general advance in pathology, we advocate the doctrine of the "toxic effect" of helminthes. Moreover, for a large number of worm diseases this hypothesis is supported by careful observations. The reflex theory is naturally not entirely rejected, but only considerably limited in its significance.

Even *Oxyuris vermicularis*, which is usually regarded as an irritating but by no means dangerous parasite, is not devoid of general effects. This is obvious from an observation of Buckler's, who found 16 per cent. of eosinophile cells in a forty-five-year-old woman, and only the presence of oxyuris to account for it. Positive observations on the capability of these worms to produce anemia have not been made, yet it is worth the attention of pediatrists to determine whether certain anemias of children are not due merely to Oxyuris vermicularis.

That *Ascaris lumbricoïdes*, in addition to its mechanical irritation, produces and excretes toxins has been proved with certainty. Huber showed that the body of the ascaris contains a substance with a pungent oily odor. This investigator experienced once, after carrying out an hour's macroscopic and microscopic examination of fresh round worms, a highly tormenting irritation of the head, neck, and hands, followd by the development of a severe urticaria on the neck and forehead, a catarrh of the right external auditory meatus, and a severe conjunctivitis. Whether it is this irritating substance which produces the anemia associated with Ascaris lumbricoides we can not state with certainty, though it is highly probable. That this parasite is the original cause in many cases of anemia is evident from the reports of Baelz, who quickly cured the anemias by removal of the worms.

[Solley reports a case of ascaris infection, with associated pernicious anemia. In another case a marked eosinophilia evidenced the general effects of the parasitic disease. A case of ascarides with marked

anemia was reported from the Jenner Hospital at Berne (quoted by Cabot), in which the red corpuscles numbered 2,480,000 before expulsion of the parasites, and two weeks after the expulsion rose to 4,200,000.—ED.]

According to Peiper, toxicity is likewise attributable to the *echinococcus*, as might be concluded from the many cases in which urticaria occurred from contact with the fluid after puncture of a vesicle. [Sabrazes[1] reports 7 cases of hydatid cysts occurring in adults. Blood-counts were obtained in 4 instances. In the first the cyst occurred in the liver. The red corpuscles were slightly reduced in number. There was moderate leukocytosis with distinct eosinophilia (1584 per c.mm., instead of 180 per c.mm.). In the second case the cyst occupied the left lobe of the liver. After an exploratory puncture there was slight fever, and during this time the eosinophilia did not exceed 1.5 per cent. Later, when the temperature subsided, the eosinophiles increased greatly, the number reaching 911 per c.mm. In the third case, one of multiple cysts, the eosinophiles numbered 694 per c.mm. In the fourth a cyst had occupied Scarpa's triangle for fifteen years. Local eosinophilia was the striking feature. In 2 other cases of hydatid cyst of the liver the eosinophiles numbered 11.81 per cent. and 17 per cent., while in the third case they numbered 4.4 per cent.—ED.] The alterations in the blood attributed to the toxic effect of trichinæ have been thoroughly discussed in the first part. Nothing positive has been determined in regard to the action of these two helminthes in the production of anemia.

Filaria sanguinis hominis and *Distoma hæmatobium* are associated with very severe anemic conditions. Both occur in the blood of man and produce severe hematuria, chyluria, and diarrhea. Their anemic action is, therefore, sufficiently explained without the assumption of toxins. [W. J. Calvert[2] refers to the occurrence of eosinophilia in a case of filariasis. The eosinophiles were largely increased in the middle of the night, and the number varied between 3 and 12 per cent.—ED.]

The most accurate and successful investigations have been done in relation to *Ankylostoma duodenale.* The well-known severe form of anemia which has been found especially in brickmakers, and has since been attributed by Griesinger solely to Ankylostoma duodenale, has undoubtedly a double pathogenesis, in that it is the result of the withdrawal of blood by the worm and of toxic substances elaborated by it. It is naturally conceivable that in any single case the anemia

[1] *Münch. med. Wochenschr.*, March 31, 1903.

[2] *Johns Hopkins Hosp. Bull.*, June, 1902.

may be entirely due to the hemorrhages or to the toxic effects. According to Leichtenstern, the first predominates in acute cases, the second in chronic, though in general an associated effect of the two factors must be assumed. That the amount of blood drawn by the parasites is not too insignificant to produce an anemia is shown by the post-mortem reports of cases of ankylostomiasis, as, for instance, those of Ernst. He describes the small intestine in 1 case as follows: "On the mucous membrane of the small intestine is an uncommonly large amount of tenacious mucus which shows here and there throughout the first meter a reddish-brown color, in the following meters a more intense color, and from the fourth meter on the intestinal contents consist of a regularly dark chocolate-brown slimy, fluid mass, the color of which is evidently due to blood. From the second meter of the small intestine to the end numerous flea-bite-like ecchymoses on the mucous membrane." According to Ernst and Leichtenstern, this hemorrhagic mass seen in the intestine consists principally of the evacuations of the worm, which sucks itself full of blood at the site of attachment. These two investigators describe further microscopic observations on living ankylostomata; "the gradually dying ankylostoma emits from its belly mouth at almost regular intervals clouds consisting of red blood-corpuscles similar to the clouds of smoke which are emitted in puffs from the smokestack of a locomotive." According to Leichtenstern, this phenomenon is observed especially in recent cases of ankylostomiasis which show severe bloody diarrhea leading to intense acute anemia and death.

[Loeb and Smith[1] have recently shown experimentally that the ankylostoma contains a substance which inhibits coagulation. This substance was found almost entirely in the cephalic portion of the parasite. This may have an important bearing on the development of anemia.—ED.]

That in ankylostomiasis the anemia may be produced by the acute or subacute losses of blood is undoubted; that it may be produced by the action of toxins is practically established. Lussana, in 1890, showed that a poisonous substance was excreted from the ankylostoma into the intestine of its host, was absorbed, and passed over into the urine. If an extract of this urine was injected into the circulation of a rabbit, an anemic condition was produced. As a control, Lussana repeated the experiment with the urine of the same person after the ankylostoma had been expelled, and showed that the urine no longer possessed this anemic effect. These experiments were later confirmed

[1] *Proceedings of the Philadelphia Pathologic Society*, June, 1904.

by other investigators. (Further experiments are necessary to show how much these conclusions lose in significance from the recent investigations of Bouchard and his pupils on the toxins in normal urine.)

The assumption of a poisonous action on the part of the ankylostomata finds further support in the metabolic experiments of Bohland. These showed a considerable increase in albuminous decomposition as well as a considerable increase in the respiratory quotient in 2 cases of ankylostomiasis. The pure post-hemorrhagic anemias, as was demonstrated above (see p. 164), are not accompanied by an increase in metabolism, while anemias due to the action of toxins are.

[E. Becker[1] has reported a case of pernicious anemia in which two Tænia saginatæ were found in the intestine. At first the parasites were considered as having no relation to the anemic condition, but as there was much gastro-intestinal disturbance, probably caused by the parasites, he thinks it probable that the anemia may have been caused by it. Anemia has also been observed in cases of infection with trichocephalus (Ostrovsky), strongyloides (P. K. Brown), and tænia solium. —ED.]

Investigations on the pathogenesis of *bothriocephalus anemia* show similar results, and the writer will, therefore, discuss it in this section, though its clinical picture is to be drawn in connection with Biermer's anemia. It was mentioned previously that the toxin theory of worm anemia (Reyher) took its origin from bothriocephalus anemia, and a number of the investigators (see Schauman) at once advocated this view. The experimental investigation of this question was first undertaken by Vlajeff, who endeavored to extract a poisonous substance from the tapeworms, but without positive results. These were first obtained recently by Schauman and Tallqvist. They made extracts or similar preparations of tapeworms in salt solution, and demonstrated on dogs (not on rabbits) that these preparations, both hypodermically and per os, possessed pronounced globulicidal properties which produced in the animals experimented on a fatal anemia. Following Ehrlich's method the investigators were able to demonstrate in test-tubes the difference between dog and rabbit blood, in that the toxin of the tapeworm produced a laked appearance in the first, but not in the second. [Regarding the effect of the bothriocephalus upon the organism, Schapiro and Dehio first suggested that destruction of the parasite and decomposition-products resulting from the same are the causes of the anemia, and base their opinion upon the finding of dead parasites in their cases. Wiltschur developed the same thought, and concluded from the altered

[1] *Deutsch. med. Wochenschr.*, September 6, 1900.

characters of the ova that the parasites were in an unhealthy state; and the discovery of cases in which there were ova but no parasites (Schauman and Neubucher) has led to the belief that the destruction and absorption of the parasite is the cause of the anemia. Some experiments have also been made to show the toxic effects of the parasite by injecting glycerin extracts. The conclusiveness of these must, however, be held as a little uncertain.—ED.]

From these examples it appears that helminthiasis plays an extremely important rôle in the origin of anemia, and that in man it is principally toxins elaborated by the worm which are responsible for it.

Anemia as the Result of Intoxication.—It is necessary to describe here, in a few words, the origin of simple anemia through intoxications in its narrow sense. The intoxications, however, which are of the greatest hematologic interest, namely, those produced by the so-called "blood toxins," in which the blood-corpuscles are directly destroyed by the action of the poison, will be discussed in the section on Hemoglobinemia.

Among the other poisons, lead is undoubtedly of the greatest practical significance in the origin of anemia. We speak frequently not only of lead gout and lead kidney, but also of "lead anemia." This is justified inasmuch as we often find in chronic lead-poisoning more or less marked anemia (Malassez, v. Limbeck). Still in these conditions we have to do with no particularly characteristic form of anemia and no direct anemic effect of the metal. The anemia is rather to be regarded as a result of the severe lesions which, according to Kussmall and Maier, are produced in the mucous membrane of the stomach and intestine.

Though seen less frequently in practice, arsenic-poisoning likewise is of considerable theoretic interest. Arsenic has undoubtedly the faculty of not only acting directly on the corpuscular elements in the blood and producing an increased and more rapid destruction of them, but also of acting specifically on the bone-marrow. According to Bettmann, changes are produced which correspond to those of simple anemia. The anemic action of arsenic is, therefore, readily obvious from these two facts. Moreover, in the clinical picture of every severe anemia, especially progressive pernicious anemia, we find conditions strikingly similar to those in arsenic-poisoning.

Other intoxications are of slight practical importance in the origin of anemia. Though, for instance, anemic conditions are occasionally observed in connection with phosphorus-poisoning, chronic alcoholism, or excessive use of tobacco, these are to be explained not by any direct

effect of the poison on the blood, but as a result of the injury to other vital organs.

[Tallqvist[1] has reported elaborate experimental investigations into the effect of toxic agents on the blood. He employed pyrogallic acid and pyridin as most suited for his investigations. Among other results, he found that after the administration of moderate quantities of the poison the development of anemia ceased and the process became stationary, or an improvement occurred unless the hemolytic agent was increased in dose. He believes the explanation of this is probably to be found in an increased hemogenic function. The effect of the poison on the red corpuscle was twofold: first, causing a degenerative change, and second, a great reduction in number. At the same time there was a leukocytosis of polymorphonuclear character; the eosinophile cells being reduced in number. The more chronic form of experimental anemia had a decided resemblance to pernicious anemia, especially with respect to the behavior of the hemoglobin during the disease as well as during the period of regeneration.—ED.]

SYMPTOMATOLOGY OF SIMPLE CHRONIC ANEMIA.

The Changes in the Blood.—In the first place, we take up the alterations which the blood itself undergoes in simple chronic anemia, since these show most accurately the deviations from the normal.

As far as the **amount of blood** is concerned, we must be content with approximations (see pages 18 and 19). In estimating this we simply make use of the finger-prick, and in accordance with the freedom with which the blood flows we speak of an increase or decrease of the entire blood. Naturally it must not be forgotten that marked variations may be readily produced by vasomotor influences or individual differences. Still, frequent experience with this procedure teaches that the amount of blood in the large group of simple chronic anemias may show marked fluctuations, a fact which is confirmed by ophthalmoscopic observation of the quantity of blood in the retinal vessels.

Still, even though a simple readily manipulated and exact clinical method of the estimation of the total amount of blood in the living person were at our disposal, the application of the results so acquired to the determination of the severity or the kind of anemia would be still problematical; for we frequently see very severe anemias with an apparently normal amount of blood in the vessels, and, on the other hand, a marked diminution of the entire amount of blood without other characteristic anemic alterations. This latter is represented by the theoretic "oligæ-

[1] *Ueber Experimentelle Blutgift Anaemieen*, Helsingfors, 1900.

mia vera" of certain writers (Stintzing and Gumprecht). Stintzing and Gumprecht assumed in their cases a diminution of the entire amount of blood, a hypoplasia of the blood-tissue, and they were supported in this assumption by the general external anemia associated with a normal number of red blood-corpuscles, a normal amount of hemoglobin, of dry substance, etc. The theoretic possibility of such an occurrence can not be excluded, yet it is more likely that these cases fall under the head of "Vascular anemia"—that is, merely an abnormal distribution of the blood.

The **color of the blood** presented by the drop issuing from the finger-prick can be distinguished from the normal by the naked eye only in advanced cases. In the severest cases the blood appears not homogeneous, but like a drop of yellowish fluid in which float reddish clouds in fine movement. This same appearance is likewise encountered in the severe cases of pernicious anemia. It is, therefore, characteristic only of a high degree, not of any particular kind of anemia.

Alterations in the staining power of the blood are much more readily estimated. It is often sufficient for an expert to observe a drop of blood on a piece of linen cloth to determine approximately the diminution in hemoglobin. Still in important cases we naturally seek a more accurate expression of the deviation from normal, and employ one of the well-known instruments (see pages 27 and 28). By such simple methods we are frequently in a position to determine a normal percentage of hemoglobin in cases where the whole appearance of the patient would suggest an anemia, even of advanced degree. Many superfluous prescriptions of iron are thus avoided and the attention of the physician is directed to the true condition, namely, neurasthenia, a gastro-intestinal affection, or phthisis.

The proof of a simple anemia is based entirely on an evident diminution of the coloring-power of the blood—that is, of the amount of hemoglobin—as determined by a sufficiently accurate method supported by control examinations. When, for instance, a normal percentage of hemoglobin is found after several examinations made independently of one another with Fleischl's hemometer, we are no longer justified in speaking of an anemia, no matter how much the external appearance of the patient would indicate it. The diagnosis of the severity of a simple anemia is likewise to be determined by hemoglobinometry, secondarily by other methods of examination of the blood, and only finally by the general symptoms. Hayem deserves the credit of being the first to consider the percentage of hemoglobin as the decisive criterion of anemia, in contradiction to the older views.

Looking over the almost numberless treatises on this subject—though the writers confine themselves here to the monographs of Leichtenstern and Reinert and the investigations of Oppenheimer and Gräber—we find the widest fluctuations from the normal. The minima observed—18 per cent., Fleischl (v. Limbeck), and 14 per cent. (Stintzing and Gumprecht)—were in cases of severe cachexia. In fact, it is the marantic conditions of malignant tumors and of chronic post-hemorrhagic processes, in which several causes act together, that show the lowest percentages; for instance, in malignant tumors we have the action of the specific toxin, of severe hemorrhages, and of ulceration.

The **counting of the red blood-corpuscles,** which was considered the most important factor in the diagnosis of diseased conditions of the blood by the older investigators, has lost value somewhat from the observation of simple chronic anemia. Cases of chlorosis especially have been observed in which with an almost abnormal number of red blood-corpuscles the percentage of hemoglobin was considerably reduced. This disproportion between the amount of hemoglobin and the number of corpuscles always was decided in chlorosis, and from recent investigations Duncan and Gräber claim that this is a characteristic of chlorosis in contrast with other anemias; further, several of these investigators even contend that a corresponding reduction of hemoglobin and blood-corpuscles is a characteristic of non-chlorotic chronic anemia. Still, it has been demonstrated in the discussion of acute post-hemorrhagic anemia (see curve, Fig. 5) that other anemic conditions besides chlorosis may show a disproportion between the amount of hemoglobin and the number of corpuscles; and further, that in regeneration the restitution of the corpuscles proceeds much more rapidly than that of the hemoglobin. Moreover, among the simple chronic anemias we find only rare cases in which the decrease in the red blood-corpuscles is as great as the decrease in hemoglobin, though the disproportion is, as a rule, not so marked as in chlorosis. From Laache's extensive investigations in cases, for instance, of secondary anemia due to pulmonary tuberculosis, it appears that the percentage of hemoglobin is on an average reduced about 22 per cent., the number of blood-corpuscles about 10 per cent. This disproportion was most striking in Laache's Case 9, in which the blood-corpuscles were somewhat increased above the normal average (5,148,000), while the percentage of hemoglobin was reduced to about 35 per cent. On closer investigation, therefore, the principle maintained by Duncan, of a correspondence of these two factors in simple chronic anemia, does not hold. In fact, the number of red blood-corpuscles can be normal even when a diminution in hemoglobin

absolutely establishes the diagnosis of anemia. Still, the number of blood-corpuscles is usually decreased, and a diminution of 50 per cent., and even more, is not rare. The most extreme case was described by v. Limbeck, and no cause for the anemia could be found except extreme poverty. The patient (a female) showed on admission 306,000 red blood-corpuscles per c.mm. (It is to be remarked that the patient fully recovered, and after seven months showed a corpuscular count of 4,280,000.)

In relation to the variations in the **specific gravity** and the **dried substance** of the blood, nothing of importance is to be added to what has been said in the general part. It was there shown that these two factors proceed hand-in-hand (even though not absolutely) with the percentage of hemoglobin, and consequently may be utilized to express the degree of the anemia. In fact, some investigators prefer the estimations of these to the direct estimation of hemoglobin, since the technic is attended with less probability of error than is that employed in colorimetry.

The relations between the percentage of hemoglobin and the specific gravity are sufficiently apparent from the tables of Hammerschlag and Dieballa (see Tables, p. 30). A disproportion occurs when the anemia is associated with albuminuria and dropsy, since in this case not only are the erythrocytes specifically lighter, but the specific gravity of the whole blood, on account of its increase in watery constituents, is diminished to a greater extent (about 4–5 per cent.) than the percentage hemoglobin.

The dried substance of the blood in anemic conditions has been investigated especially by Stintzing and Gumprecht, Maxon, and Biernacki, who determined that in the condition which has been described as simple chronic anemia, its decrease is almost proportional to the degree of the anemia. The same was found by v. Jaksch in regard to the percentage albumin determined by the Kjeldahl method. There is no variety of anemia which can be differentiated by a peculiarity of the dried substance, and this fact teaches us that in the large series of simple chronic anemias, not different kinds, but only different degrees of pathologic alterations are to be differentiated.

A few statistics from Stintzing and Gumprecht will show the maximum deviations of the dried substance from the normal (21.6 per cent. in men, 19.8 per cent. in women). The maxima in this instance are likewise to be found in malignant tumors—*e. g.*, in several cases of gastric cancer (in women). With a hemoglobin percentage of 14 (Gowers), the dried substance amounted to 8.6 per cent.; with 15 per

cent. of hemoglobin and 1,400,000 blood-corpuscles, to 9 per cent.; with 18 per cent. of hemoglobin and 1,900,000 red blood-corpuscles, to 9.9 per cent.

In regard to the percentage albumin of the entire blood, which normally amounts to 22.62 per cent., v. Jaksch found as a minimum, 8.46 per cent. (dried substance = 9.9 per cent.) in an anemic with carcinoma ventriculi.

Only one single physical method of examination has recently shown qualitative differences in the blood of etiologically different anemias, namely, the separate estimation of the specific gravity and of the dried substance of the blood-serum.

As was mentioned in the first part, the serum is characterized by a notable constancy in its dried constituents in comparison with the entire blood. This was demonstrated by Hammerschlag in a series of investigations on more than 400 patients. Nevertheless, in the very recent literature is found a communication from Askanazy, in which he declares that almost all cases of anemia show an increase of water in the serum; though Hammerschlag, v. Limbeck, and Grawitz insist that there are only isolated cases of simple anemia in which the law of constancy of the composition of the serum is violated. For instance, Hammerschlag found in a severe anemia of unknown origin a hemoglobin percentage of 15 (Fleischl) and an erythrocyte count of 1,700,000, with the specific gravity of the entire blood 1032.5 and of the serum 1031; in other words, in spite of the advanced anemia, no trace of hydremia in the serum; while in a considerably less severe anemia, following hematemesis, with 25 per cent. hemoglobin and 1,400,000 corpuscles, the specific gravity of the serum was reduced to 1022. Grawitz also found in post-hemorrhagic and post-inanition anemias an evident reduction of the specific gravity of the serum. The same is unanimously asserted by all writers to be true in cases of nephritis associated with dropsy, and C. Schmidt claims a diminution in the albumin of the serum in all conditions in which there is a copious excretion of albumin by the intestine—*e. g.*, dysentery.

The question whether fluctuations occur in the percentage proportion of the different albuminous constituents (albumin and globulin) of the serum has, as far as the writers know, not been definitely determined. According to v. Limbeck, the normal fluctuates within wide limits (globulin, 16.9–38.2 per cent.; albumin, 61.7–83.1 per cent.); and the single case of anemia (its true nature not further described) examined by this investigator and Pick showed figures which fell within these limits.

[Faville[1] has brought forward some evidence that there is an augmentation of the proportion of globulins after hemorrhage.—ED.]

The blood ash has been frequently studied in anemic conditions. Statistics relative to this are found in the much-quoted older works of Becquerel and Rodier, as well as in the recent works of Biernacki, Moraczewsky, and Coenen. Looking over the careful analyses of these investigators, we find no constancy in the results which would justify us in drawing conclusions on the pathology of anemia. Becquerel and Rodier themselves analyzed an immense number of cases, and found such contradictions that, on account of the finding in a single case of chlorotic blood, they are more inclined to assume a considerable error in technic than to believe their own figures correct. It seems, indeed, as if in hematologic methods the difficulty and care required stand in inverse proportion to the value of the results obtained.

Becquerel and Rodier state that the percentage of iron in anemic blood is invariably diminished proportionately to the degree of the anemia. The normal average of 0.565 iron to 1000 gm. blood stands in constrast to the average of 0.366 obtained from 30 cases of anemia. Biernacki, whose normal averages agree very well with those of the two French investigators, states that he found a normal percentage of iron several times in anemic conditions, especially in chlorosis.

The writer wishes to mention a recent communication of Jolles, who investigated several cases of chlorosis and anemia with the aid of his previously described ferrometer.[2] The amount of iron in the blood is most readily expressed in percentages of the normal ("ferrometer estimation") similarly to the amount of hemoglobin. Jolles found in 2 cases of chlorosis with 70 and 55–60 per cent. hemoglobin, respectively, ferrometer estimations of 76.1 and 61.1; in other words, a pronounced correspondence. The serum was free from iron in these cases, as it should be physiologically. Yet 2 cases of "anemia"—a more accurate description is unfortunately wanting—showed percentages of hemoglobin of 28 and 15, and ferrometer estimations of 68.6 and 41.7. Moreover, in these cases the serum contained iron, though in quantities too small to be estimated. It is probable that an important rôle in clinical hematology will yet be played by the ferrometer.

According to Biernacki, anemic blood is differentiated from normal by an increase in water, sodium, and chlorin, while the potassium salts, iron, and phosphates are diminished. The reduction of potassium was most marked in every case. Biernacki's statements in regard to the

[1] *Arch. p. l. Sci. Med.*, 1890, xiii. [2] Reichert, Vienna.

percentage of phosphorus and chlorin have been confirmed by Moraczewski.

The experiments recently done by A. v. Korányi on the osmotic pressure of the blood and urine in different diseases, seem to promise much. It is not possible to go into detail, yet it may be stated in reference to the blood, that one result of the investigation showed the lowering of the freezing-point of the blood to be very slight in the majority of cases of anemia. Deviations from this occur only when the anemia is complicated by disturbances either of respiration or of urinary secretion, conditions which are characterized by a considerable lowering of the freezing-point.

The **coagulability of the blood** and its separation into serum and coagulum was studied by Lenoble, a pupil of Hayem's, with the object of discovering how anemic blood behaved. He found evident differences in comparison with the normal in severe cases of anemia and chlorosis. Clotting, which normally took about ten to twenty minutes, lasted in severe cases (number of blood-corpuscles less than 1,000,000) on an average from five to ten minutes. The separation of the serum and clot, which begins normally about twenty-five minutes after withdrawal of the blood, and terminates in four to six hours, began in isolated cases of severe symptomatic anemia after ten, eighteen, and twenty minutes, and terminated in thirty-five minutes, seventy minutes, and at the latest in three hours.

Lenoble's numerous complete protocols demonstrate that these two phenomena of clotting and separation of serum show a remarkable correspondence to the degree of the anemia. In the section on Progressive Pernicious Anemia the writer refers to the differential diagnostic value of these two factors.

The **degree of alkalinity** of the blood has been likewise frequently investigated in anemic individuals. The older literature, with its innumerable contradictions, may be entirely omitted since A. Löwy has shown the inadequateness of previous methods, especially the employment of opaque blood. Löwy's method of titration of the laked blood has been recently accepted by even the clinicians; in fact, C. S. Engel endeavored by an especially constructed "alkalimeter"[1] to estimate the alkalinity of the blood from very small amounts (0.05 c.c.), though A. Löwy considers the results obtained by this method to be doubtful.

[The method of Löwy may be described briefly as follows: 45 c.c. of a 0.2 per cent. ammonium oxalate solution are placed in a 50 c.c. flask; 5 c.c. of blood are added and mixed with the oxalate solution,

[1] Leitz, Wetzler.

which prevents coagulation and lakes the blood. The mixture is then tested with a $\frac{1}{25}$ normal acetic acid solution, using 5 c.c. of the mixture for each test and lakmoid paper as the indicator. Neutralization is indicated by the development of a red zone at the edge of a drop of the fluid on the lakmoid paper.

Engel has devised a convenient apparatus for clinical purposes, the advantage of which consists in the fact that sufficient blood is obtained from the ordinary puncture. The blood is measured and diluted in a pipet similar to those used for blood-counting, but much larger. In this 50 cm. of blood are diluted with 5 c.c. of distilled water. This mixture is titrated with $\frac{1}{75}$ normal acetic acid (1 gm. acetic acid to 1 L. of water). The indicator used is lakmoid paper.

The normal alkalinity of the blood as determined by this method has varied between 450 and 500 mg. of NaHO, according to Löwy and Engel. Strauss, however, obtained lower figures—between 300 and 350 mg.; and Brandenburg with a slightly modified method found 330 to 370 mg. as normal limits.—ED.]

With this now generally recognized method, Löwy himself, among others, examined several cases of anemia. Without any statement as to the degree or the variety of anemia he gives the following figures:

In health:
447.68–508.96 mg. NaOH to 100 gm. blood.
In anemia:
Case 1: 675.2.
" 2: 555.2 (with only 11 per cent. dried substance in the blood).
" 3: 504.48.
" 4: 360.0 mg. NaOH to 100 gm. blood.

K. Brandenburg worked with the same method, and found the alkalinity decreased in all cases of anemia (normal 330 to 370 mg., NaOH to 100 gm. of blood); for instance, in a puerperal case that had become very anemic during pregnancy, 212 mg.; in a case of anemia produced by actinomycosis of the abdominal organs, 202 mg. Brandenburg found in all cases the amount of albumin of the blood diminished to a corresponding degree.

It is evident that these two series of observations are very contradictory. Löwy found in 3 of 4 cases a high normal or increased alkalinity; Brandenburg, a decided decrease. Löwy shows in 1 case a high alkalinity with an extremely low percentage of dried substance; Brandenburg asserts on the basis of his observations a correspondence between the alkalinity and the dried substance.

These contradictions demand further investigation, to which will also fall the problem of discovering the significance of alkalinity in the

pathology of anemias and the relations between it and the other chemic and physical properties of the blood.

[A. Lumière, L. Lumière, and H. Barbier[1] have investigated the value of the titration method for determining the alkalescence of the blood. They point out that the determination of alkalescence by titration gives uncertain results, because when any acid is added in excess and the excess then determined by titration with an alkali, a certain amount of the acid remains in combination with organic bases, etc. They propose a method by which the comparison between the weight of blood and of acid is observed, and in which titration with iodin is used instead of a colorimetric method. Von Rigler[2] has studied the question of the total alkalinity of the blood and of that of the blood-serum in various conditions. He determined the alkalinity by Fodor's method, and found that the blood in all cases was able to combine more acid than the blood-serum. He found that the action of micro-organisms, of which he tested 11 pathogenic varieties in 63 experiments, was constantly in the direction of a decreased alkalinity affecting both the total blood and the serum. The reduction in alkalinity was greatest in cases of fatal infections, though not necessarily in the rapidly fatal forms. Bermin[3] has contributed some observations on the alkalescence of the blood as determined by Tscherbakoff's modification of the method of Landois, and in 12 healthy persons he found the alkalescence 0.182 to 0.218 gm. of NaHO. There was a reduction in cirrhosis of the liver, jaundice, pulmonary tuberculosis, bronchitis, asthma, chronic rheumatism, chronic interstitial nephritis, malaria, leukemia, anemia, chlorosis, diabetes, gout, and obesity. These observations agree with those of others, excepting that Peiper and Jacob and Graeber found an increase in alkalescence in chlorosis. Bermin found in 9 cases a decided decrease, which increased in 6 of them during the administration of iron in proportion to the increase in hemoglobin and the number of red corpuscles.

Dare has recently devised a method and an alkalimeter for carrying it out which seems to promise useful results. The instrument consists of a capillary tube (of a capacity of 15 mg. of blood) which, passing through a stopper, fits in a graduated pipet, the upper end of which is expanded and has a minute opening for the entrance of air. A medicine-dropper, marked to contain 2 c.c. and fitted with soft rubber tubing, is used to expel the blood from the capillary pipet.

[1] *Arch. de Méd. expérim.*, 1902, xiii., 6, p. 791.
[2] *Centralbl. f. Bakteriol.*, 1901, xxx., 22–25, p. 823.
[3] *Zeitschr. f. klin. Med.*, 1900, p. 365.

The capillary tube is filled from a drop of blood obtained by puncture and is then placed in the pipet held vertically. The blood is then forced through, and into the tube with distilled water from the medicine-dropper, and water is added until the mixture reaches a point marked zero in the pipet. The opening in the pipet is covered with a finger and the blood and distilled water thorougly mixed. The dropper is then filled with an acid reagent composed of tartaric acid (Merck) 0.075, alcohol (94 per cent.) 20 c.c., distilled water q. s. ad 200 c.c. The acid solution should be slowly added until the absorption bands of oxyhemoglobin disappear from the blood mixture, the test being made with a Browning's pocket spectroscope. The amount of acid solution required is noted on the scale of the pipet and the alkalinity can be computed from the following table:—

Scale of Equivalents Computed from a Basis of 15 mg. of Blood to 2 c.c. of Acid Solution ($\frac{1}{200}$ of the Normal).

C.c. of reagents.	Milligrams of NaOH to 100 c.c. of blood.
2.6	345.0
2.4	319.0
2.2	292.0
2.0	266.0
1.8	239.0
1.6	212.0
1.4	176.0
1.2	169.0
1.0	133.0
0.8	96.0
0.6	79.0
0.4	53.0
0.2	26.6—Ed.]

The anomaly of the blood which constitutes the essence of anemia, the diminution of hemoglobin, is likewise visible in the **morphologic appearance of the red blood-corpuscles.**

In order to recognize microscopically a slight decrease in hemoglobin (about 10 per cent.) it is not sufficient to limit one's self to the examination of the fresh blood, but the stained dried preparations must be brought into service. We observe then, especially in preparations stained with eosin, pretty considerable differences in the staining of the red blood-corpuscles (see also p. 47). In the first place, we see, in addition to the discs, which show by their staining a normal amount of hemoglobin, much less intensely stained cells. In the second place, the physiologic concavity, which in the normal red blood-corpuscle is indicated by a somewhat greater transparence, or at most by a complete absence of central stain, becomes decidedly more conspicuous. The less the amount of hemoglobin in the corpuscle, the more the coloring-matter is retracted from the center, till in very marked cases only a

small stained ring surrounded a comparatively large colorless disc is left ("pessary forms," Litten). It must be remembered that individual cells show the impoverishment in hemoglobin to very different degrees, and that in the same field erythrocytes with a normal amount of hemoglobin may be found alongside of extreme pessary forms. The oligochromemia is naturally then to be estimated not from the impoverishment of individual cells, but from a general survey of the preparation which notes whether the cells with a normal amount of hemoglobin predominate, or are in the minority, or whether only cells showing a loss of hemoglobin are to be found. In high grades of anemia with a hemoglobin per cent. of 30, 20, or under, we sometimes find not a single cell with a normal appearance, but pessary forms exclusively, in which even the ring may take the stain but feebly (see Plate I., Fig. 2).

Polychromatophilic or *anemic degeneration* is also evident in the blood-discs, even in mild cases of anemia, though neither the number of degenerated cells nor the intensity of the degeneration corresponds so exactly with the degree of oligochromemia as the behavior of the cells to stains. The anemic degeneration may be more pronounced in cases with high percentages of hemoglobin than in severe anemic conditions. The determination of the factors on which these differences are directly dependent by a number of comparative examinations would be in many ways an important and interesting study.

Poikilocytosis—*i. e.*, a deviation from normal size or shape—is a symptom peculiar to all kinds and degrees of anemia, and even in mild cases both forms of poikilocytes are encountered. Nevertheless in simple anemias the blood-corpuscles undergo changes in size in only one direction, namely, toward diminution, never toward enlargement.

Isolated blood-corpuscles under the normal average (about 7.5 μ) also occur in normal blood, but in anemic blood they actually predominate in number. In advanced cases of anemia, normal sized red blood-corpuscles may be entirely wanting. The smallest red blood-corpuscles, the microcytes, have a diameter of only about 2 μ.

The changes in shape are likewise more pronounced the more advanced the general oligochromemia. In conditions showing very low percentages of hemoglobin we may find scarcely a single corpuscle of normal shape, every distortion imaginable being evident. Still, individual corpuscles may show on staining a normal amount of hemoglobin, even though they are abnormal in size and shape. Moreover, the fact that the concavity remains in the poikilocytes, goes to prove their full functional capability (Ehrlich). (See Plate I., Fig. 2.)

Though the morphologic abnormalities described in the two preced-

ing sections are apparent in every preparation of anemic blood and in numbers corresponding more or less to the severity of the disease, this is not true of the nucleated blood-corpuscles. The occurrence of these depends neither on the severity of the anemia nor its causation—that is, the manner of its origin. In one form of simple anemia, namely, acute post-hemorrhagic, erythroblasts are found in a relatively large number of cases and apparently with a certain regularity (see p. 160). In other chronic cases, however, their occurrence, as far as our present knowledge is concerned, is absolutely irregular. In the same case they may be present one day and absent the next without any other alteration of the blood or the general condition; and further, among several cases of anemia of equal severity and the same etiology, one may show nucleated blood-corpuscles, the other not. Though, from all that we know about the erythroblasts, we must assume that their appearance in the blood is a sign of increased reparation due to increased activity of the bone-marrow, we can not say what irritant attracts them into the circulation.

In simple chronic anemias we encounter, as a rule, only one form of nucleated red blood-corpuscles, namely, normoblasts; though in rare cases—*e. g.*, of traumatic anemia—microblasts. If in a large number of blood examinations now and again a megaloblast is found, this is to be regarded only as an extremely rare exception which might possibly be explained by the further history of the patient.

The behavior of the **white blood-corpuscles** in simple anemic conditions is but little characteristic for the anemic process *per se*, and is almost always dependent on the cause of the blood alteration or complications. In the pure form of acute post-hemorrhagic anemia the stimulation of the bone-marrow due to the impoverishment of blood is evidenced by a greater or less polynuclear hyperleukocytosis. In the simple chronic anemias, however, the influences acting on the white blood-corpuscles are so numerous that it is impossible to determine in individual cases to what degree the deviation from the normal is dependent on the anemia. Still, when we compare a large number of cases, noting especially the analogy of erythrocytic regeneration, we are forced to conclude that in simple chronic anemia also the bone-marrow is stimulated to increased work. We see consequently, in practically all cases of simple chronic anemia, an increase in the polynuclear neutrophiles, though the extent of the increase is very variable and stands in no relation to the degree of the anemia.

This relation is best illustrated by the behavior of the *eosinophile cells.* In simple chronic anemias every degree of eosinophilia is en-

countered. If a neutrophile hyperleukocytosis or a marked general increase in leukocytes occurs, the percentage of acidophiles may be very low; but if the proportion of the white to the red blood-corpuscles deviates but little from the ordinary, the number of eosinophiles is, as a rule, high (normal 4 to 6 per cent.). When a more marked eosinophilia is seen, it must be regarded not as the result of the anemia, but of other specific causes, such, for instance, as helminthiasis.

In a recent very careful study of the *blood-platelets*, van Emden showed that a moderate increase occurs in anemic conditions, especially chlorosis. Instead of the normal number of 180,000 to 256,000, he found them increased to 558,000, and in one anemic child with a splenic tumor to 829,000. The increase in blood-platelets, however, is by no means constant, and holds apparently no relation to the severity of the oligochromemia. As demonstrated first by Hayem, a regular increase in blood-platelets is particularly evident in post-hemorrhagic conditions.

General Symptoms and Symptoms Manifested by Special Organs.—Simple chronic anemia, as was shown in the first section, is extremely complicated in its pathogenesis, and in regard to many of its important features is still inexplicable. The problem, therefore, of determining whether certain anatomic and functional alterations of the individual organs are in any way characteristic of anemia, is extremely difficult and at times impossible. There are two factors especially which require the most careful consideration before any anomaly in the general organs or tissues should be attributed to the action of the anemia; namely, first, whether these anatomic or physiologic alterations preceded the anemic condition or developed under its influence; second, whether they correspond with the anemia; in other words, whether they are the result of the same primary pathologic processes. A criterion for the solution of these questions is found in the study of the purest form of anemia, namely, the acute post-hemorrhagic, and this is, therefore, placed at the beginning of this work; though observations on uncomplicated cases of chlorosis are of almost the same value in this regard.

The alterations regularly encountered in these two diseases may be justifiably considered "anemic" when seen in other cases of simple chronic anemia. Nevertheless, although the possibility can not be *a priori* denied that certain anomalies not observed in acute post-hemorrhagic anemia or chlorosis are characteristic symptoms or sequelæ of the anemia, we must first determine whether in a number of cases of chronic anemia of like pathogenesis and severity they are regularly or comparatively frequently found, and, further, whether in the case of

causes which sometimes but not always produce anemia, they occur even when the blood is not affected.

In the description of the **general disease-picture** of simple chronic anemia we may borrow the general features of the description of acute post-hemorrhagic anemia.

Still, in the external appearance of advanced cases a difference is manifested between the two groups, inasmuch as the pallor of the **skin** in acute anemia is rather whitish in contrast to the yellowish tint of chronic anemia.

If we compare acute and chronic anemia of equal severity, we find that the latter manifests a less pronounced **muscular weakness**—in fact, only in very severe cases do we see complete muscular exhaustion. Nevertheless, all conditions, even the slight ones, show a ready fatigue not only of the muscles, but of the nervous system, of the organs of special sense, and even of the mechanism controlling intellectual activity. In addition very many individuals manifest a marked oversensitiveness and irritability of these functions, for which Immermann suggested the characteristic and generally adopted name of "irritable weakness" ("reizbare Schwäche").

In considering the special symptomatology of simple chronic anemia, the writers will frequently refer to what has been previously said in order to avoid repetition. The tendency to **edema** is usually more pronounced in chronic conditions than in acute, likewise the tendency to **hemorrhages.** Since the latter are the result of alterations (fatty degeneration) of the vessel-walls, they usually occur only after the anemia has existed a long time. The rapid recuperation in acute cases prevents the occurrence of these alterations, and consequently of the hemorrhages. In chronic conditions, however, we find almost regularly, hemorrhages of every kind in the shape of very small foci in the skin and mucous membranes, especially of the mouth, stomach, and intestine, in the central nervous system, the retina, and the serous membranes. Since they sometimes lead to severe losses of blood by epistaxis, hematemesis, etc., they exercise a dangerous counter-effect on the anemia.

[Thomas Houston[1] has made some observations on the edema of anemia that are of interest here. The absence of reduced weight in anemics he holds is due to accumulation of fluid in the blood and tissues. If this were deducted, there would probably be found the same loss of weight in anemic patients as in those suffering from other chronic diseases. In the case of anemias, especially chlorosis, the first

[1] *Brit. Med. Jour.*, June 14, 1902.

step seems to be a ridding of the system of the excessive fluid. In pernicious anemia a gain in weight is usually significant of an unfavorable prognosis when the hemoglobin does not at the same time improve. Occasionally, however, it is the precursor of improvement. The edema of anemia, he thinks, results from hydremic plethora.—ED.]

The condition of **general metabolism** in acute anemia is a criterion of its state in simple chronic anemia. Under the complicated conditions present, to attribute the abnormalities found in individual cases of chronic anemia to the anemic condition *per se* is, to say the least, hasty, since the unknown effects of a primary disease or a complication may be responsible. Positive conclusions as to metabolism in anemia can be drawn only from the study of acute anemia and chlorosis. From these we find, contrary to previous views, that there is no anomaly of metabolism which can be considered characteristic of an oligochromemia or any anemic condition. The difficulty mentioned above of deciding whether symptoms associated with chronic anemia are to be considered as due to the anemia *per se*, is never so evident as in disturbances of the **digestive tract.** Diseases of the intestinal tract and anemia very frequently exist together, and the question, which of the two is primary and which secondary, can be decided only rarely from the anamnesis, the subjective symptoms, and the objective examination. Chlorosis, for instance, is a striking example. This is associated in the majority of cases with digestive disturbances, and it is frequently impossible to say whether it is the cause or the effect of these disturbances.

Certain criteria are furnished, first by the sequelæ of acute post-hemorrhagic anemia, and secondly by observations which show that certain gastro-intestinal disturbances, though frequently seen in anemia, are incontestably of other origin.

The behavior of the *appetite* is variable, and is undoubtedly more dependent on the primary disease or the cause of the chronic anemia than on the anemia itself. Sometimes anemic patients go to meals with a normal or even increased appetite, but even then satiety quickly occurs. Other cases manifest a continuous lack of appetite which can not be combated by otherwise effective appetizers. It will be shown later that there is no anomaly of secretion to explain this loss of appetite. It may be considered, therefore, an associated symptom of the general reduction of energy peculiar to anemia.

The appetite is also frequently influenced by painful sensations which are aroused by the introduction of food, even so-called "light" food. These painful sensations may be also independent of the introduction of food, certain areas being spontaneously painful or

especially tender to pressure, or a general diffuse sensitiveness of the whole gastric region may exist. We sometimes see very severe paroxysms of cardialgia. In such cases, according to Boas, we must think of slight losses of substance in the mucous membrane. In fact, the pain may be sufficient to arouse the suspicion of an ulcus ventriculi even apart from the symptom of hemorrhage, when the treatment corresponding to it should be instituted.

The oversensitiveness of the stomach may express itself besides in an easily excited nausea.

Exact investigation of the gastric functions in anemia shows a diminution of the *hydrochloric acid* in but a small number of cases (Ritter and Hirsch). According to the investigations of v. Noorden and others, the hydrochloric acid is excreted in normal amounts, or is even increased in pure cases of chronic anemia. All the investigators (v. Noorden, Boas, and H. Herz) found the motor function of the stomach completely undisturbed. When motor weakness of the stomach, therefore, is found associated with anemia, this must be attributed to other causes.

In reference to the *intestinal function*, the material at hand is very scanty. *A priori*, the frequent very good nutritive condition of anemics would show that marked disturbances of intestinal activity can scarcely be attributed to the anemia *per se*. v. Noorden, to whom we owe the most numerous and complete investigations of this subject, demonstrated that, contrary to the generally received opinion, no diminution of the intestinal secretion exists even in cases of advanced chlorosis. Moreover, he found the fat in the feces quite as completely broken up as in health, a proof of the normal excretion of pancreatic juice.

Under the direction of the same observer, Lipmann-Wulf undertook investigations on *absorption* in anemia. He showed that in severe cases of chlorosis the fat absorption may be poor, but that in others equally severe there was no deviation from the normal.

The absorption of dry substances and albumin is, according to v. Noorden, almost always normal.

v. Noorden further criticised the assertions of previous writers that an increase of albuminous decomposition was a peculiarity of severe anemic conditions. His pupil, Rethers, reports that pretty frequently, but by no means regularly, aromatic products of albuminous decomposition occur in very large quantities in the urine of chlorosis.

The *motor function of the intestine* is frequently diminished in anemics, and obstinate constipation is common to every kind of anemia; in fact, certain observers (see p. 200) see in it a direct effect of the anemia; still

we find often enough, even in severe anemia, entirely regular evacuations.

A further discussion of the special symptomatology of simple chronic anemia is unnecessary since it would only be a repetition of what has been said in relation to acute anemia. The writer wishes only to refer to several symptoms which for a time were regarded as especially characteristic of progressive pernicious anemia, and which are likewise found in simple anemias of severe grades, namely, retinal hemorrhages, fatty degeneration of the heart, degenerative conditions of the brain and spinal cord, and atrophic alterations of the stomach and intestinal mucous membrane. The complete description of these interesting alterations is, for evident reasons, reserved for the section on Progressive Pernicious Anemia. Nevertheless, the writer must insist that they are by no means peculiar to Biermer's disease, but are also seen, even though comparatively rarely, in the very severe forms of simple anemia. In fact, a direct connection between the severity of the anemia and the occurrence of these degenerations by no means exists; on the contrary, we seem to have to do with differences in the pathogenesis, since of several cases of equally severe simple anemia one will manifest these symptoms, the other will not.

Moreover, reference may be made to the section on Progressive Pernicious Anemia for the anatomic findings in simple chronic anemia, among which special importance can be attributed only to the changes in the **bone-marrow**. There is not sufficient material at hand to say with certainty how often and under what circumstances the lymphoid transformation of the marrow of the long bones takes place in simple chronic anemia.

DIAGNOSIS.

The diagnosis of simple chronic anemia can usually be made from the general clinical symptoms; still, on account of the previously mentioned abnormalities in the distribution of the blood ("vascular anemia"), the diagnosis should be made secure in any doubtful case by estimations of the hemoglobin. Moreover, in all cases of severe anemia, especially those in which the cause is not recognizable, a careful morphologic examination of the blood is indispensable.

The most important diagnostic consideration, the differentiation of simple and progressive pernicious anemia, will be discussed under the latter heading (see p. 311).

THERAPY.

The treatment of simple chronic anemia is completely successful only when its cause can be found and combated. If a definite etiology is

found in any case, all treatment directed toward the anemia alone may be omitted and the special indications applicable to this case followed.

In cases, however, in which the anemia continues after the primary disease or the cause of the anemia is removed, or in cases of unknown origin, medical treatment must be directed against the anemia itself. The principal points in the treatment have been indicated in discussing acute post-hemorrhagic anemia.

Chronic anemia requires, in the first place, complete physical and mental rest, and in severe cases this should be obtained by even weeks in bed and the greatest possible isolation.

No general principles of nutrition are specifically applicable to anemia since its metabolism is in no way peculiar. In individual cases the diet is determined by the general nutritive condition of the patient judged from the functional power of the digestive organs. A special preference is given on the menu card of every anemic to vegetables, especially green vegetables and fresh fruit, and among these we may mention particularly spinach, asparagus, apples, and strawberries on account of a relatively high percentage of readily assimilable iron.

Climatic treatment of simple chronic anemia is indicated in many cases. As a matter of fact, the requirement that work be given up completely can be fulfilled in no better way. A sojourn in the mountains has often a rapid and decided effect on the general torpidity of anemics, and certain theoretic investigations of late years indicates that possibly the blood-making organs themselves are stimulated by the elevation. Robust patients may without fear sojourn in the mountains up to 2000 meters. Feeble patients will do better at a medium elevation (300 to 900 meters). A sea climate, especially when cool and dry, together with sea baths, is a splendid stimulant for robust anemics.

In cases that are not too advanced hydrotherapeutic measures in the shape of mild cold water rubbings and douches may be employed; still it must be remembered that anemics are very sensitive to severe cold.

The most important medicament in simple chronic anemia is iron, the administration of which has been thoroughly discussed in the preceding section. In every protracted or especially severe case the iron therapy should be combined with general treatment as indicated. If it is not successful after four to six weeks, arsenic should be substituted. The specific effect of arsenic on the formation of blood and its method of employment are explained in the section on Progressive Pernicious Anemia. The striking results frequently achieved by a combination of iron and arsenic in chlorosis naturally make their combined use worthy of recommendation in other anemic conditions.

I did not mark this section with ink. I presume the original owner did - Dr George Clements, a practising physician at Crawfordsville, Ind.
This is the only section marked in the complete American edition of twelve (12) volumes
HCB.

PROGRESSIVE PERNICIOUS ANEMIA.

DEFINITION.

BIERMER'S celebrated discourse in the year 1872, in which the name "progressive pernicious anemia" was employed for the first time, constitutes the beginning of our knowledge of this subject and undoubtedly gave the impulse to the numerous subsequent investigations and communications. This service of Biermer's has been generally recognized even by those who came forward after the discourse with more or less justifiable claims to priority. While referring for historic details to the excellent monographs of H. Müller and Eichhorst, the writer would like to call attention to the fact that Lebert in 1853, and Addison in 1855, described severe anemic conditions which they expressly differentiated from others as a special form ("essential anemia," "idiopathic anemia"). Still, it was Biermer's communications of 1868 and 1871 that first succeeded in making general the knowledge which had up to that time been limited to a few scientists.

[Walter Channing[1] first described cases of severe anemia (pernicious anemia) in association with the puerperal state and diseases of the uterus; and made the condition familiar to New England practitioners of his time.—ED.]

On account of its great historic importance and its concise yet clear description, the liberty is taken of introducing Biermer's discourse word for word. The report in the *Correspondenzblatt für schweizerische Aerzte*, Jahrgang 11, 1872, No. 1, reads as follows:

"Prof. Biermer made a report on a form of progressive pernicious anemia frequently observed by him which is ordinarily associated with fatty processes in the circulatory apparatus, and as a result with capillary hemorrhages in the skin, retina, brain, the meninges, and other serous membranes. Biermer has been investigating the peculiarities of this disease for five years, and in the autumn of 1868 gave a preliminary report at the Dresdener Naturforscherversammlung. Since then the number of his observations has increased to 15, so that it may be said this disease is not rare in the Canton of Zürich. It occurs

[1] *New England Quarterly Jour. of Med. and Surg.*, Boston, 1842–43.

in poor people, especially in women, at about the thirtieth year; besides bad sanitary conditions, the puerperium seems to play a rôle. Still, it also occurs in younger and older individuals of both sexes. The youngest patient was a girl of eighteen, the oldest a man of fifty-two. Insufficient and unsuitable nourishment, unsanitary dwelling conditions, protracted diarrheas, sometimes hemorrhages, precede the disease and seem to favor its development. According to the observations so far made, the most frequent forerunner is chronic diarrhea with or without gastric disturbances. Chlorosis seems to precede it but rarely, and a spontaneous commencement without an evident etiology is likewise exceptional. The disease has no connection with affections of the spleen or with malaria. The only organic disease which so far seems to be responsible for the origin of the anemia in several cases is follicular ulceration of the large intestine.

"The symptoms are as follows: 1. Anemic-hydremic appearance. Marked pallor, emaciation, but no atrophy of the subcutaneous fat as in carcinoma and phthisis. Frequently a yellowish-white color without icterus. In advanced stages slight edema of the loose subcutaneous tissue of the face, feet, and hands; sometimes ascites. 2. The ordinary anemic nervous symptoms, weakness, vertigo, palpitation, etc. 3. Digestive disturbances with consequent complete anorexia; indigestion, sometimes a sensation of pressure in the stomach; frequently occasional diarrhea. 4. Circulatory symptoms, murmurs over the heart and vessels, the former so marked as to give rise to the suspicion of valvular defects. The murmurs are systolic in time, though once a diastolic murmur was added to the systolic without any valvular disease being found post mortem. At the base the systolic murmur is usually rougher than over the ventricle, where it is more blowing. The heart-murmurs are not always found from the beginning, but come on during the course and become stronger. Over the cervical arteries murmurs and sometimes frémissement. The latter once also over the jugular vein, which likewise showed in 1 case evident pulsation, all without valvular defects. When the heart action is rapid, the beat diffuse, and the dulness enlarged by a slight hydropericardium, as repeatedly happens, the picture becomes very similar to that of heart disease, and on account of the fever frequently present it may be confused with endocarditis. Section, however, shows nothing of this kind, but only a partial fatty degeneration of the heart-muscle. The heart action is as a rule hastened, the heart-beat diffuse, wavy, and feeble. 5. Fever is unimportant, though it is observed transiently in almost all cases, sometimes very slight in character, sometimes more marked, but with-

out special type and short in duration. In 1 case the fever simulated typhoid for a time, and the physician recommended the patient to be isolated. Ordinarily the fever is insignificant and without cause, and has, therefore, been briefly designated in the clinic as anemic fever. Prof. Biermer conceived a humoral cause for the fever, though he also considers it possible that small internal hemorrhages and disturbances of digestion may be the causes. Evident local causes for the fever could not be found. 6. The retinal apoplexies almost always found are interesting. They were discovered even in cases in which there was no subjective complaint of visual disturbances, and in which the visual tests proved negative. When they were wanting in the first stage they usually appeared later. These retinal hemorrhages were naturally evident post mortem, and were of striking appearance. 7. Hemorrhages into the skin, small petechiæ, were more rare. Hemorrhagic urine and epistaxes were observed only once, albuminuria very exceptionally. 8. Scattered capillary hemorrhages were found in the brain on the internal surface of the dura and in the pia several times without characteristic symptoms during life. One patient succumbed to a large capillary cerebral hemorrhage. Another patient experienced sudden pain in the right arm and leg, scanning speech, right hemiplegia (including face), but all the symptoms disappeared in half an hour. Delirium frequently occurred toward the termination of life.

"The course showed in all cases a chronic increase of the anemia and hydremia, an appearance and augmentation of heart symptoms, accidental capillary hemorrhages, hydremic effusions, occasional fever, eventual anorexia, and often diarrhea. Pneumonia and erysipelas were rare final complications. A fatal termination occurred in all cases except one which was somewhat improved.

"On section Prof. Biermer found, in addition to the universal anemia, almost always partial fatty degeneration of the papillary muscles and the small vessels, which, on the one hand, explains the heart-murmurs, on the other, the capillary hemorrhages. The fatty degenerated papillary muscles appeared spotted with yellow or marmorated, and the muscle of the ventricular wall and the septum often showed a similar appearance. Marked degeneration of the cardiac musculature was, however, exceptional. In the large arteries there was nothing abnormal or, at most, very small areas of fatty degeneration of the intima, while in the small arteries of the kidneys, for instance, fatty degeneration was not uncommon. Fatty degeneration of the capillaries, especially of the brain, was frequent. Extravasations of spider-web thinness found on the internal surface of the dura in 3 cases showed no association

with pachymeningitis. The speaker, therefore, considered them hemorrhages dependent on the fatty metamorphoses in the capillaries. The capillary apoplexies of the brain, the retina, the epicardium, and pericardium were also considered dependent on the nutritive disturbances of the capillary walls. Biermer considers that this last, as well as the fatty degeneration of the heart-muscle, is the result of the altered composition of the blood, analogously to the fatty degenerative processes so frequently seen in the tissues after interruption of the arterial circulation. Liver, spleen, and kidneys showed nothing striking."

Under this symptom-complex, therefore, Biermer comprehended essential, idiopathic, primary anemia, as well as the anemia with known etiology and pronounced secondary character; at least, in several cases he expressly points out an organic disease, follicular ulceration of the large intestine, as the starting-point of the disease. Insistance on this is not superfluous, since recent writers have made a separation of progressive pernicious anemia into primary and secondary.

All the investigations which since Biermer's time have been devoted to progressive pernicious anemia, even those which contest the propriety of placing it under a special pathologic head, are directly or indirectly, consciously or unconsciously based on Biermer's communication. Through these the boundaries of progressive pernicious anemia have experienced many alterations. At the beginning the functional and anatomic disturbances of the heart, the fatty degeneration, and the retinal hemorrhages were considered pathognomonic. Moreover, after the careful work of clinicians had discovered these symptoms both separately and together in cases which could not be differentiated from the ordinary secondary anemias, other "specific" characteristics of progressive pernicious anemia were found, which were likewise dethroned after a short time. Poikilocytosis (Quincke), microcytosis (Eichhorst), the transformation of the fat-marrow of the long bones into lymphoid marrow [Pepper] (Cohnheim), were all found in cases of simple anemia after they had been discovered through investigations of progressive pernicious anemia, and were thus deprived of their pathognomonic significance.

These experiences resulted in many observers (Eichhorst) determining the diagnosis of progressive pernicious anemia from negative facts alone. Only anemias with a progressive severe course advancing without complication to death, in which the autopsy showed no organic disease apart from that belonging to anemia *per se*, were recognized as progressive pernicious anemias. This conception is probably appropriate to the essential form of the disease, but is contrary to the sense

of Biermer's definition, which comprehended conditions originating from or complicated with an organic disease. Moreover, on the completion of further observations a sharp distinction between the so-called essential forms and those of secondary character was found to be forced and untenable.

A solid basis for the definition of progressive pernicious anemia was first found when the immense gap in Biermer's work was filled by an exact description of the blood-changes. The gathering together of the separated members of this group under one head should indisputably be credited to the methods of studying the histology of the blood. Several of the blood alterations peculiar to progressive pernicious anemia, the specificity of which will be more accurately proved in another section were, at least in part, mentioned in the older observations of Hayem, Eichhorst, Laache, and H. F. Müller. Still it was Ehrlich's work that clearly defined them, and showed their decided significance for progressive pernicious anemia. According to the investigations of Ehrlich and his predecessors, a typical case of progressive pernicious anemia shows a more or less large number of red blood-corpuscles of more than the normal size, while in simple anemias the erythrocytes are normal in size or smaller. The appearance in the blood of megalocytes as well as of their nucleated preceding stages, indicates that the regeneration of the blood no longer proceeds in a physiologic way; in other words, we have not to do with a mere increase of physiologic regeneration similar to that observed in simple anemia, but the blood formation itself loses its physiologic character throughout a greater or smaller extent of the bone-marrow, and following a type which is never normally seen in adults simulates the formation of blood in the embryo.

These characteristics, showing as they do a profound functional alteration in the most important blood-making organ, namely, the bone-marrow, sharply separate the anemias in which they are found from all others. Moreover, they are so striking that they demand a differentiation of the megalocytic and megaloblastic anemias from the normocytic and normoblastic, even though this classification does not exactly correspond to Biermer's.

Defining the boundaries of our subject, therefore, we have to do with a disease showing the characteristics described by Biermer and Ehrlich. These will naturally be more thoroughly discussed later. Still, we must remember that we are not considering a disease *sui generis*, but a frequently occurring syndrome arising in connection with very different affections.

OCCURRENCE, CAUSATION, AND ORIGIN.

Since the attention of physicians was first directed to progressive pernicious anemia, it has been frequently observed, and can now scarcely be regarded as a great rarity. In Berlin, for instance, in the medical wards of the three large city hospitals, 148,000 patients in round numbers have been treated within the last ten years; among these the diagnosis of progressive pernicious anemia was made 274 times, in other words, in about 2 per cent. of all internal diseases.

There is undoubtedly a variable predisposition to the disease in different places. As is well known, it occurs especially frequently in Zurich and its immediate vicinity, where Lebert, Gusserow, and Biermer collected their first observations. In contrast to this, in Munich and Prague, according to Weigl and Klebs, the disease is very rare, so that these cities seem to possess a relative immunity. On what these local differences depend is at present unknown. Explanations based on differences in nutrition are only the offspring of our embarrassment, for the better conditions of life asserted to exist in Munich are evidently not the reason, since the disease is not rare in individuals in the most favorable material circumstances.

From the first large series of statistics collected by H. F. Müller, it appeared that the female sex was affected much mere frequently than the male. From more extensive monographs and personal observations, the writer has collected 240 anamneses of progressive pernicious anemia in order to test this assertion. These showed 130 female and 110 male. Among the previously mentioned 274 cases in the three large city hospitals in Berlin (from the yearly reports of 1887 and 1888 to 1897 and 1898) 172 were in females, 102 in males, though it must be added that the female divisions of these hospitals have somewhat smaller accommodations than the male. This large series of statistics, therefore, would seem to confirm H. Müller's statement that females possess a greater susceptibility.

[In three series of American cases the preponderance in the male sex contrasts strikingly with German statistics:

	Male.	Female.
Cabot	57	53
McCrae, McPhaedren	48	14

These figures correspond very closely with the editor's own experience. Bristowe and Osler also found the disease more common in males. —Ed.]

The *age* at which both sexes are most frequently affected comes in

the so-called "best years." From the anamneses of the previously mentioned 240 cases, we find:

In the first decennium	1 case.
" " second "	22 cases.
" " third "	61 "
" " fourth "	67 "
" " fifth "	47 "
" " sixth "	33 "
" " seventh "	7 "
" " eighth "	2 "

Though the third and fourth decennia, therefore, are particularly exposed to the disease, old age and youth are not entirely exempt. The case mentioned in the first decennium was an eight-year-old girl in whom the disease followed severe gastro-intestinal disturbance (H. Müller). Monti and Berggrün report from the literature and from personal observation, 16 cases of progressive pernicious anemia in children; 2 of these were nurslings, 5 were between one and five years of age, and 9 between five and fourteen. It is to be remarked, however, that the diagnosis of progressive pernicious anemia can not be made from the morphologic appearance of the blood in early life, because during this period insignificant diseases show deviations from the normal, which, if observed in adults, would mean a very serious prognosis. [Robert Hutchinson[1] has recently investigated the occurrence of pernicious anemia in childhood, and after stating that its great rarity has been noted by all systematic writers, quotes Rotch, who found not a single case among 2000 children below the age of two at the Infants' Hospital in Boston. Hutchinson himself searched the records of the Hospital for Sick Children, Great Ormond Street, for one in vain. He has collected from the literature the cases published as pernicious anemia, 11 in number, of which 5 seemed to him probably genuine.—Ed.] Of the 2 cases in the eighth decennium that have been recorded, 1 was a man of seventy-three, in whom no definite cause could be found (Laache), the other a woman, likewise seventy-three, who succumbed to a bothriocephalus anemia (Schauman).

As far as the writer knows, there is no evidence in the literature that *heredity* plays any rôle in the origin of the disease. The report by Sinkler and Eshner quoted in all books, of 3 cases of essential anemia in one family, is so incomplete that it is useless. Schmaltz quotes an observation of Klein's, who saw a brother and sister succumb to progressive pernicious anemia.

No characteristic differences were found as far as the constitution of

[1] *Lancet*, May 7-14, 1904.

the patient was concerned. Robust healthy individuals seem to be as frequently and as severely attacked as the delicate.

As far as social and hygienic connections are concerned, the percentage of those in well-to-do circumstances is rather too high than too low.

In order to study the factors which from the standpoint of our present knowledge play a rôle in the origin of progressive pernicious anemia, we will take up first a group of pernicious anemias, in which the etiology, even if not the pathogenesis, may be regarded as completely explained, namely, the "**bothriocephalus anemias.**"

F. A. Hoffmann, Botkin, Reyher, first, and later many others (for special literature, see Schauman), drew attention to the frequent occurrence of the bothriocephalus in cases of progressive pernicious anemia and ascribed to this parasite the etiologic rôle. The theory was opposed by a few investigators on the ground that the occurrence of Bothriocephalus latus is very frequent, progressive pernicious anemia relatively rare, and further that patients sometimes show an enormous number of worms (70 to 80) without becoming anemic. This fact, that a disease excitant may occur in one individual as a harmless parasite producing no pathologic symptoms, is not without analogy. Pathogenic bacteria (diphtheria bacilli, pneumococci, etc.), the virulence of which was proved by animal experimentation, have been not infrequently found in healthy living bodies without any evidence of a pathologic effect. The most convincing proof, however, of the etiologic significance of Bothriocephalus latus is shown by the frequently observed rapid and complete recovery from the severe anemia after removal of the worm.

The identity of bothriocephalus anemia with progressive pernicious anemia was for a time contested by many, among them Biermer himself, but this dispute has been recently settled by the close resemblance of the anamnesis and post-mortem reports. Moreover, since Schauman has shown by careful microscopic investigations that bothriocephalus anemia possesses also the characteristics demanded by Ehrlich, we have every reason for designating bothriocephalus anemia as progressive pernicious anemia with known etiology.

Still, even when we acknowledge the fact that the bothriocephalus can produce a genuine progressive pernicious anemia, we have not determined how the worm acts. The statement that severe anemias are found in only a small number of infected individuals has been frequently confirmed. Moreover, the severity of the disease stands in no relation to the number of worms. The infection itself, therefore, does not produce the anemia. Further, since the individual affected shows no particular characteristics which can be regarded as especially predis-

posing, we must assume something else in the behavior or in the properties of the parasite which transforms it from a comparatively harmless inhabitant of the intestine into a highly dangerous disease excitant.

Among all the theories so far proposed, the best supported is that which assumes that it is not the healthy living parasite, but the diseased or dead one which proves so dangerous to its host. Schapiro was the first to express the conjecture that on disease or death of the worm poisonous substances were elaborated, the absorption of which led to anemia. With this in view, Wiltschur examined twelve worms, the removal of which completely cured severe anemias. "In all cases the worms were either dead, decomposed, or sick. I determined the presence of disease from the eggs, which had undergone marked alterations. In one case of very severe anemia the removed worm was so decomposed and emitted such a nauseous odor that in spite of the carbolic acid solution in which it was placed, it required considerable determination to continue the examination. On the ground of these observations the assumption seems probable that the bothriocephalus is capable of producing severe anemia only when sick or dead. Moreover, the severity of the disease depends on the degree of decomposition; in other words, the amount of such products absorbed."

The most weighty objection against this theory is that severe anemias also occur in cases in which the parasite is found living and fresh in the intestine. Yet, this loses in significance with the observations of Schauman, Neubecker, and others, who describe typical anemias in cases in which no parasite was discovered either by purgation or post mortem, though the eggs of the bothriocephalus were found in the evacuations. That the worm itself must have been present in the intestine a short time before the appearance of the eggs in the evacuations, can not be doubted therefore. When in spite of careful investigation no proglottides could be found in the intestine (as has occurred in several cases), we are forced to the conclusion that the worm died and was completely absorbed. Nothing now stands in the way of the assumption that even when the parasite is living and well an absorption of dead and decomposed proglottides may occur. The objection against the very clear theory of Schapiro and Wiltschur is, therefore, readily removed. [Bard[1] reports 2 cases of pernicious anemia due to bothriocephalus. In one the blood-count showed 1,100,000 red corpuscles, 7000 white corpuscles, 30 per cent. hemoglobin. After removal of the parasite with filix mas the red corpuscles rose to 2,800,000 and the hemoglobin to 45 per cent. In the second case the parasite was probably removed a

[1] *Semaine Méd.*, Juillet 23, 1903, xxii. 30, p. 241.

year before. For various reasons, however, the author believed this case was one of bothriocephalus anemia. It terminated fatally.—ED.]

As mentioned previously, Schauman and Tallqvist have brought forward positive evidence for the theory of the toxic effect of Bothriocephalus latus. They extracted the body of the worm with salt solution and obtained a substance which had a marked globulicidal effect on the blood of dogs. In one case, for instance, it produced within two weeks a decrease in the number of blood corpuscles from 7,200,000 to 3,200,000, not to mention other symptoms of severe anemia, such as marked pallor of the mucous membranes, intense exhaustion, soft heart murmurs, etc. The autopsy on the animal which succumbed to exhaustion, showed in addition to general anemia of the organs, a marked iron reaction in the spleen and liver. The investigators make no definite statements as to the morphology of the blood in these experiments.

Though it is very desirable that these investigations be repeated in large numbers, they furnish very definite evidence concerning the pathogenesis of bothriocephalus anemia. It is to be conjectured that the parasitic toxins demonstrated by animal experiments can exercise their hemolytic effect on human blood, and this continued destruction of blood-corpuscles naturally leads to anemia. Moreover, the fact that the bone-marrow, at least in man, does not respond as in other losses of blood by an increased production of normal cells, but takes on the type of megaloblastic blood formation which is abnormal to the adult organism, shows that the parasites do not necessarily first produce anemia, but are capable of acting directly on the blood-making organs.

Our satisfactory comprehension of the etiology of bothriocephalus anemia becomes of considerable value in the study of progressive pernicious anemia in general. The observations on bothriocephalus anemia are of service in all chapters of its pathology, and even in its therapy. Schauman's felicitous and valuable work on this subject is, therefore, of general importance. There is no question that clinicians who have the opportunity to see bothriocephalus anemia frequently are in a particularly favorable position to solve the burning questions of progressive pernicious anemia with an accuracy that could otherwise be obtained only by animal experimentation.

In the first place, the question is still in dispute whether it is necessary or even permissible to separate progressive pernicious anemia from other anemic conditions. Those who scruple about this see in progressive pernicious anemia only a difference of degree. They refuse to accept the special designation "anæmia perniciosa," and replace it by "anæmia gravis," thereby rejecting every qualitative differentiation of

Biermer's anemia from simple chronic anemia, of melagocytic from normocytic. Though this question will be brought up in another section, the writer would like to show here how valuable the knowledge of bothriocephalus anemia is toward its solution.

Schauman reports several cases which from their general symptoms, the number of blood-corpuscles, and the percentage of hemoglobin can not be regarded as severe, but at the most as moderately severe cases of anemia. In spite of this they showed microscopically Ehrlich's characteristics of progressive pernicious anemia in a most pronounced way just as do even very severe cases. The results and observations in this regard have yet to be completed, slight cases especially must be examined and accurately described. Still in the writer's opinion our present knowledge is sufficient to justify the conclusion that it is the toxin, and not a simple anemia produced by the worm, which causes the characteristic abnormalities of the bone-marrow; that much misused word "specific" is completely justified in its application to this effect.

In a recent work Grawitz designates the cases which are cured by removal of the worm as "simple secondary anemia," and only those cases which proceed to death in spite of removal as "true progressive pernicious anemia." This determination of the nature of the disease from the prognosis seems to the writer strained on account of the complete similarity of the clinical and hematologic pictures. The difference between the two is evidently not essential, but only one of degree. The limit at which the prognosis becomes absolutely bad can be definitely decided no more than in any other form of progressive pernicious anemia or simple anemia. When, therefore, in two cases of equally severe bothriocephalus anemia, one is cured and the other proves fatal, there exists between them the same difference as between two cases of equally severe acute post-hemorrhagic anemia, of which one recuperates after the cessation of the hemorrhage, while the organism of the other, especially as far as the new formation of blood is concerned, can no longer produce the energy necessary for the retention of life or recuperation. Moreover, if we accept Grawitz's division of bothriocephalus anemia, we must also make a division between fatal and non-fatal cases of post-hemorrhagic and other anemias. From the cases published in the literature the writers—since unfortunately they have never had the opportunity of personally observing bothriocephalus anemia—draw the conclusion, therefore, that the bothriocephalus under definite, though not yet fully understood circumstances, is capable of causing an anemia which presents the definite characters of a Biermer-Ehrlich anemia. Moreover, he insists again

that even the mild cases show a clinical and hematologic stamp which differentiates them from simple chronic anemia.

Unfortunately we must even to-day acknowledge that our experiences in regard to bothriocephalus anemia constitute our entire positive knowledge in regard to the etiology of progressive pernicious anemia. From the beginning certain views were stated as to the cause of this disease, but these were based in part on accidental occurrences, from which generalization proved unjustifiable, or which on more careful study aroused serious question as to whether the symptoms previously regarded as causal were not simply associated or even secondary.

One group especially was separated by all previous writers, namely, **progressive pernicious anemia following pregnancy and childbirth.** These cases are to a certain extent historically important, for even before Biermer's publication Lebert, and especially Gusserow, described cases of severe anemia in pregnant women which to-day, after a study of the anamneses and post-mortem findings, we can class with progressive pernicious anemia in spite of the fact that no thorough hematologic examinations were made. [The cases described by Channing in New England in 1842 have been referred to before.—Ed.] These cases, of which Eichhorst was able to collect 29 in his monograph, can be advantageously divided into subclasses: 1. Those which suffered from severe inanition during pregnancy on account of severe vomiting and diarrhea; 2. Those in which the anemia seemed to have been produced by hemorrhages from the nose, varicose veins, etc., during pregnancy, or by severe loss of blood during delivery; 3. Those in which the pregnancy ran its course without disturbances of nutrition or hemorrhage, and yet an anemia arose during pregnancy and progressively advanced to death, even after the delivery was brought about in the eighth month. The first two subclasses can be readily reckoned with the anemias of inanition and hemorrhage, but in the third a special influence of pregnancy must be assumed. The most likely conclusion is that pregnancy leads to pernicious anemia through the extraordinary demands made by the growing fetus on the maternal organism. Birch-Hirschfeld refers the damage to the blood from products of decomposition arising from the placenta, which cause first a modification of the plasma, and this in turn an injury to the blood-cells. Lebert sees the explanation in nervous influences. Nevertheless, on account of the extremely small number of cases, it is impossible to believe that pregnancy has any specific power to produce progressive pernicious anemia or create a predisposition to it.

Moreover, it appears to the writers strange that in the recent litera-

ture we find scarcely any reports of progressive pernicious anemia in the anamnesis of which pregnancy or the puerperium played a rôle. This may be partly due to the fact that the symptoms are now so generally known that doubtful cases are no longer published. Though Eichhorst in 50 cases of progressive pernicious anemia in females attributed 29 to pregnancy and childbirth, the writer can find among 26 cases in females from his own experience and from the literature (Grawitz, Laacke, Fr. Müller, Haarth, Plümecke, Dorn, Koch) only a single case in which a connection between the disease and a previous pregnancy could be assumed (Laache, Case 9). The recent text-books on obstetrics mention progressive pernicious anemia, as far as the writer can see, only with regard to the older works of Gusserow and others. Ahlfeld expressly insists that he never observed such a case. Moreover, the majority of Eichhorst's cases (22) are taken from the publications of Swiss investigators. This would seem to indicate with considerable certainty that for this frequent occurrence of anemia during pregnancy in Switzerland, especially in the Canton of Zurich, local influences were responsible, a conjecture which was expressed by Gusserow in his first publication. The nature of these influences is absolutely unknown, in fact, it is possible that we have to do with temporary factors. Still, there is no longer reason to consider certain cases of progressive pernicious anemia "a special disease of pregnancy" or to attribute the origin of the disease to a particular influence of the pregnancy.

[Elder and Matthews[1] report 2 fatal cases of pernicious anemia following labor. The first case occurred in a woman of twenty-nine years, who became severely anemic three weeks after a normal labor. An abscess of the breast initiated the anemia, which was typical in the general features and morphology of the blood. The second case occurred in a woman thirty-one years old two weeks after her second labor, which was instrumental, but unattended by severe hemorrhage. Ulceration of the tongue and throat initiated the anemia. The clinical symptoms, condition of the blood, and autopsy findings were typical. The authors remark on the rarity of such cases in recent literature—Ed.]

Apart from the special group of pregnancy anemias the cases of progressive pernicious anemia may be classified with reference to their etiology exactly as we classify simple chronic anemia. We find progressive pernicious anemia frequently:

1, following repeated or long-continued hemorrhages;

2, after poor nourishment, bad sanitary conditions, overwork, etc., have destroyed the health;

[1] *Lancet*, Aug. 8, 1903, p. 152.

3, following other diseases, especially of the digestive tract, syphilis, malaria, or typhoid fever.

Since the writers wish to avoid superfluous repetition, they will refer to the explanation which was given in regard to the action of these factors in the production of simple chronic anemia. They showed there that the influence of these factors in the production of anemia, though it is not to be doubted, requires further elucidation. Still, since the same influences have been frequently observed in the previous history of progressive pernicious anemia, they will state: A progressive pernicious anemia may develop as a result of any influence capable of producing a simple anemia. [Ralph Stockman[1] contributed a notable article on the probable nature of pernicious anemia. According to his view, the pernicious character is brought on by repeated small hemorrhages, which in turn result from a fatty degeneration of the blood-vessels. It is these multiple small hemorrhages which, in his opinion, convert a case of anemia from a more or less benign to a malignant or pernicious character.—Ed.] We meet simple anemia in its different stages with a frequency corresponding to a certain extent to the distribution of its causes, while in comparison cases of progressive pernicious anemia are extremely rare. We see innumerable cases in which the health has been undermined on account of poverty develop simple anemia as a consequence, yet how very few in comparison develop progressive pernicious anemia. The same is true of hemorrhages, and of different organic and constitutional diseases. What other circumstances must coincide in order that the same causes which produce simple anemias by thousands may lead to progressive pernicious anemia?

The answer most frequently given to this question is, that there is only a difference of degree, in other words, that progressive pernicious anemia, represents only the most marked form of anemia, the further augmentation of a simple anemia, is certainly the easiest; still, it leaves unanswered important objections. In the first place, we not infrequently see simple anemias advancing to stages which many cases of progressive pernicious anemia fail to reach, hemoglobin percentages under 20 and 15, and blood-corpuscles under 500,000. Nevertheless, in spite of the extreme severity of these two symptoms, the microscopic examination of the blood shows a picture very different from that in even milder cases of progressive pernicious anemia. Comparing the blood-picture of extreme cases of both, the difference between them is so striking, as is evident from the special descriptions of the symptomatology of the blood, that

[1] *Brit. Med. Jour.*, 1894, vol. i.

even the inexperienced may recognize it. Both simple anemia and progressive pernicious anemia show different stages. We recognize, for instance, mild and severe cases of simple anemia, and "mild"—*i. e.*, beginning and severe cases of progressive pernicious anemia. Still, the second can not arise from a simple anemia merely by augmentation of intensity, and when a progressive pernicious anemia develops on the soil of a simple anemia a new disease is actually added.

The nature of this process, however, is entirely unknown. The view taken from the analogy with bothriocephalus anemia, that the metamorphoses of the bone-marrow function must be referred to the irritation of toxic substances, lacks every support in many cases of "progressive pernicious anemia post anaemiam simplicem." In explanation of progressive pernicious anemia from simple anemia, Stockman called attention to the alterations found in the capillaries, especially of the internal organs in isolated cases of simple anemia, and claimed that the hemorrhages resulting from this degeneration were the actual cause of the origin of the pernicious form.

Syphilis.—In the communications on progressive pernicious anemia during the last two years, it is to be remarked that in a large number of patients a preceding syphilis could be demonstrated by the history, the clinical examination, or at the autopsy. From the material so far at hand it can not be decided whether there was a genetic connection between the two or only an accidental coincidence. Even when we omit the older statistics—in Eichhorst's large collection, for instance, we discover only one case in which a connection with syphilis could be conceived—and take up only the recent ones from the time of Fr. Müller's publication, when the attention of clinicians was especially directed to this point, we find that the cases in which syphilis preceded an undoubted progressive pernicious anemia are by no means common. On account of the extremely wide distribution of syphilis[1] we must be careful of drawing too general conclusions from statistics. At any rate, a much larger amount of material is necessary than is at present available.

Moreover, the demonstration of the causal significance of syphilis in progressive pernicious anemia "ex juvantibus," as has been attempted in several cases by Fr. Müller, can not be regarded as conclusive. Even though anti-syphilitic treatment improves a few cases, especially as regards the anemia, improvement is so frequently seen after admission to a hospital that the influence of the mercury or iodids is very

[1] H. Neumann found that among all the patients of the Moabit Hospital, in Berlin, at least 22.4 per cent. had had syphilis.

difficult to recognize. Moreover, Laache found in one case in which syphilis was evident, and in which he considered a connection between the progressive pernicious anemia and the syphilis as probable, that anti-syphilitic treatment was not only not effective, but even injurious, while arsenic was of benefit, as it is in some other cases.

From an etiologic point of view the numerous cases of progressive pernicious anemia in which clinical and anatomic **disturbances of the intestinal tract** are manifest deserve special attention. In the discussion of simple anemia it was shown that anemia based on digestive disturbances is to be explained partly by the relative inanition and partly by the absorption of toxic substances or by a combination of both. The origin of the progressive pernicious anemia by absorption of toxic substances from the intestinal canal is supported principally by bothriocephalus anemia, and to some extent by certain therapeutic procedures. For instance, Sandoz claims to have "cured" one case of progressive pernicious anemia by continued washing out of the stomach, Jürgensen one by energetic evacuation of the intestine. Still the evidence of such observations is only conditional on account of the frequency of apparent cures when they are only transitory remissions.

[It is proper to allude in this place to the experimental investigations of Wm. Hunter, which showed the probable gastro-intestinal origin of toxic substances that cause the disease in certain cases. More extended reference to Hunter's work will be made elsewhere.—ED.]

How much importance in an etiologic way must be attributed to the **atrophic processes** in the gastro-intestinal wall will be discussed more thoroughly in another section (see p. 286). Here the writer will only say that they seem to be less the cause of the anemia than coincidental symptoms or even effects of it.

The relation of **tumors** of the gastro-intestinal tract, especially carcinoma of the stomach, to progressive pernicious anemia is very different. That these tumors more frequently than anything else produce the most severe anemic conditions, there is no doubt. The severe cachexia to which a long-protracted gastric cancer leads, on account of its marked disturbance of nutrition, its hemorrhages, the production of injurious fermentation in the stomach, and its own specific toxicity, is invariably associated with a deterioration of the blood; in fact, the lowest percentages of hemoglobin and the lowest corpuscular counts have been found in advanced cases of this very kind. By far the majority of these cases, however, show microscopically the evident character of a simple chronic anemia, and further, the intensity of the anemia usually stands in more or less direct relation to the degree of the cachexia.

True, in a few very advanced cases we see on repeated examination an occasional megalocyte and megaloblast, though the general impression received from the microscopic picture remains unchanged. The carcinoma usually proves fatal before the blood formation has assumed to any considerable extent the megaloblastic type.

In contrast to these may be placed several rare cases which have been frequently mentioned in the text-books, yet only rarely described and given their proper significance. The writer refers to those cases which during life run their course under the typical picture of a Biermer-Ehrlich anemia, and in which the post mortem shows, apart from the lesions corresponding to the anemia, a gastric carcinoma associated with total or partial atrophy of the gastric mucous membrane. One of these cases observed during life by v. Noorden, and diagnosed by him as progressive pernicious anemia, was examined post mortem by O. Israel. In this case a tumor the size of a large cherry-stone, which proved on microscopic examination to be carcinoma, was found immediately below the small curvature one and a half inches from the pylorus. The subcutaneous fat in the body was described as "of fair amount" (ziemlich reichlich). The symptoms of the anemia had been pronounced six months before death. The writer has had the opportunity of seeing two such cases. In one (case H) he diagnosed progressive pernicious anemia on the ground of the clinical and microscopic picture. To his surprise he found at autopsy a ring-shaped fibrous carcinoma of the pylorus without ulceration which had given no symptoms during life. He saw a short time ago a further case with Prof. Renvers, who has kindly allowed him to mention it. This was quite similar to the preceding one; clinically and microscopically a genuine progressive pernicious anemia, which showed on section a carcinoma the size of a hazelnut on the greater curvature.

While we see in those cases (which require further investigation) the association of progressive pernicious anemia and carcinoma ventriculi, death is apparently attributable to the anemia on account of the extremely small size of the tumor and the splendid condition of nutrition of the patient. Yet Israel assumes in his case that the anemia must be attributed to the tumor in spite of its small size, since this was the source of frequently repeated hemorrhages. The remains of such hemorrhages were still to be seen microscopically in the neighborhood of the tumor. Nevertheless, the writer is still inclined to believe that the carcinoma was secondary to the progressive pernicious anemia, and that the small hemorrhages correspond to those frequently encountered in different organs in progressive pernicious anemia, though

they certainly may have hastened the exitus in this one case. [The editor has observed a case of typical pernicious anemia in association with cancer of the stomach in which the clinical course seemed to indicate that the anemia was undoubtedly secondary to the gastric disease. Several cases have been reported in which the autopsy showed metastatic lesions of the bone-marrow, and associated with these megaloblastic or lymphoid transformation of the marrow so distributed as to suggest that the cancerous deposits were the direct cause of the marrow changes. In the light of these cases it seems probable that cancer is one of the numerous conditions that may occasion pernicious anemia. Frese[1] reports a case of metastatic carcinoma of the bone-marrow with severe anemia. The primary growth was in the stomach, and metastases in the lymph-glands, lungs, medulla, and pons were discovered. In a second case he also found metastases in the bone-marrow, with a blood-picture resembling that of pernicious anemia.—Ed.] W. Fenwick has called attention to the not uncommon association of atrophy of the stomach and gastric cancer. On the other hand, as will be discussed later, there is a close connection between atrophy of the gastro-intestinal mucous membrane and progressive pernicious anemia. The connection between progressive pernicious anemia and carcinoma is, therefore, evident.

From the preceding we may conclude that the relations between progressive pernicious anemia and carcinoma ventriculi are of two kinds. In the first place, there are cases of gastric carcinoma in which a progressive pernicious anemia develops on the soil prepared by the severe cachexia and anemia; and in the second, there are cases of progressive pernicious anemia in which a favorable soil is created for the development of a carcinoma of the stomach possibly through the medium of the atrophy of the mucous membrane. In the latter cases the carcinoma usually produces no clinical symptoms, as the symptoms are at most slight.

Alterations in the bone-marrow occupy a very special place in the etiology of progressive pernicious anemia. That the almost regular transformation of the fatty marrow into functional red lymphoid marrow has nothing to do with the etiology of the disease, is at present generally acknowledged. Nevertheless certain cases of severe, sometimes primary, sometimes secondary, metastatic affections of the bone-marrow have been reported which resembled clinically genuine progressive pernicious anemia. Some of the cases, it is true, were reported at a time when microscopy of the blood did not meet our present requirements. Among these may be mentioned the frequently quoted cases

[1] *Deutsch. Archiv. f. klin. Med.*, Sept. 27, 1900.

of Litten and Waldstein in which multiple foci of suppuration and tumor-formation were found throughout large areas of the bone-marrow with consequent alterations of it. Recently, however, several thoroughly investigated cases in which blood examinations were regularly made over a long period have been reported. Among these may be differentiated two groups, the first including a case of sarcomatosis of the bone-marrow described by Ehrlich and P. Grawitz, and Nothnagel's well-known case of "anedenia ossium." In these two cases the bone-marrow function was completely obliterated so that it did not show even a megaloblastic new formation of blood. In spite of their close clinical similarity to progressive pernicious anemia, the writers would not at the present day be deceived on account of the characteristic alterations of the blood being absent. In the second group may be placed two cases, one from v. Leyden's clinic, very thoroughly described in a dissertation by G. Lazarus; the other, observed by I. Epstein under the direction of Neusser. On account of the marked deviation of the blood-picture from that of progressive pernicious anemia, the clinicians made only a conditional diagnosis of Biermer's disease in both cases, and this hesitancy was confirmed by the autopsy, in that tumor-formations were found in the bone-marrow. These extremely rare cases, the significance of which has been discussed earlier, serve to explain many contested points in regard to the function of the bone-marrow and the occurrence of lymphoid metamorphosis, though they contribute in no way to the etiology of progressive pernicious anemia.

In conclusion, we have still to take up the cases of progressive pernicious anemia, in the anamneses of which not a single positive etiologic factor can be found, and in which the clinical examination and the autopsy show no organic changes that might be responsible for the severe disease. These forms were previously described as "primary" or "essential"; in fact, some writers still regard them exclusively as progressive pernicious anemia, and consider their separation from other anemic conditions both justifiable and necessary. These diseases remained for a long time an enigma and gave rise to numerous theories, till through the study of bothriocephalus anemia we learned to understand the origin of at least one of them. To-day the majority of authorities believe that on the further advance of our knowledge the whole group will be deprived of their designation "primary anemia." This idea was appropriately expressed by Birch-Hirschfeld.

[Hunter has recently advocated the infectious origin of pernicious anemia. He believes there is a direct relation between infectious (streptococcic) disease of the tongue and upper alimentary tract and

pernicious anemia. Others have failed to find the conditions he describes. G. A. Charlton,[1] however, has studied experimentally the effects of chronic infection with the bacillus coli and reaches the following conclusions:

"From the above epitome of the conditions found it will be observed that in these experiments there has been developed a very remarkable state of advanced anemia. That anemia is not quite comparable with any of the classic forms seen in man. In some respects it is strikingly like the condition of pernicious anemia, namely, in the very great diminution in the number of erythrocytes, the marked poikilocytosis, and the appearance of nucleated red corpuscles.

"As far as I know at the present time no other observer has produced these striking conditions. But, on the other hand, it differs from pernicious anemia in the fall of the amount of hemoglobin being parallel with the decrease of the red corpuscles; in the absence of a distinct Quincke's siderosis, or increased presence of iron in the livers; in the absence of any clear evidence of inflammatory or other disturbances of the digestive tract, and of well-marked changes in the bone-marrow.

"Whether employment of other strains of the colon bacillus would lead to a picture more clearly resembling pernicious anemia, or whether again the employment of bacterial toxins rather than the pure attenuated cultures, will give different results, must be left for future studies. In the meantime I am inclined to think that the observations here recorded are of a certain value, as indicating one method, namely, that of 'subinfection' by the ordinary bacterium of the digestive tract, whereby a very definite grade of anemia may be produced."

These experiments were suggested by the studies of Adami[2] on latent infection and "subinfection."—ED.]

Kryptogenetic Pernicious Anemia.—It is not to be doubted that among them there are several varieties which at their base and even in their pathogenesis are very different from one another, and that possibly in addition to intoxication, infections, and nervous and trophic disturbances, are capable of producing the Biermer-Ehrlich symptom-complex.

Many investigators have pronounced for the infectious nature of kryptogenetic pernicious anemia, or at least, some of its forms; Klebs, for instance, on account of observing flagellates in the fresh blood in advanced stages of the disease; Frankenhaüser and Petrone on account of leptothrix forms found in their cases; Bernheim, on account of a

[1] *Jour. of Med. Research*, viii., No. 2.
[2] *Jour. Amer. Med. Assoc.*, 1899.

bacillus found in the blood in one case post mortem; Perles, on account of small strongly refractive corpuscles with active movement which he saw in the blood in several cases, though he has himself questioned their parasitic nature. All of these observations have met the same fate in that after they had been reported by their discoverers, they were not confirmed either by themselves or other investigators. Hayem's warning—not to be deceived from the examination of fresh blood in a case of progressive pernicious anemia by the extremely lively motility of the microcytes—contains the essential criticism of the observations just mentioned.

With the lack of physical grounds for a sufficient explanation of the origin of progressive pernicious anemia, we can not deny that psychic influences may be responsible in some cases. If we investigate the previous history of a patient, it is only natural to assume that we shall find in the great majority of cases some occurrence or other which produced intense emotion, and which can be brought into contemporaneous connection with the beginning of the disease. Curtin, for instance, reports the cases of two female patients, who after a sudden very severe mental shock, failed to recover, became anemic, and finally, four years later without further complication, succumbed to the anemia. In a third patient with a similar event in her life, Curtin describes only the severe disease without theorizing on its origin. If, like Curtin, we wish to find a connection between the development of the anemic condition and the psychic alteration, it is much simpler to see the direct cause of the anemia in the disturbances of nutrition, which frequently develop in just such cases, than in the completely unknown psychic influences on blood formation or blood destruction, for which we have no analogy.

SYMPTOMATOLOGY.

ALTERATIONS OF THE BLOOD.

Biermer's previous description of the general disease-picture makes it superfluous to detail it again unless we wish to repeat the same thing in other words.

In the discussion of the special symptomatology, the blood is the first thing that attracts our attention. It is striking that in the first comprehensive monograph on progressive pernicious anemia (H. Müller) the description of the alterations in the blood observed during life takes scarcely more than a secondary position, while to-day the hematology is of the greatest interest on account of the great advances it has made.

The quantity of blood is in the majority of cases decidedly di-

minished. Frequently on a deep prick only one small drop of blood issues forth, and even on strong pressure no other can be forced from the same wound, so that sometimes several pricks must be made to fill the pipette of Gowers' apparatus. Still occasionally the blood flows so copiously from the wound that it is difficult to stop the hemorrhage. This behavior corresponds in no way with the severity of the other blood symptoms. In fact, the writers have observed that in the course of improvement it becomes more difficult to obtain the amount of blood necessary for the making of a dry preparation or for the estimation of the hemoglobin than during the worst stages of the disease.

[J. L. Smith has determined the volume of blood in severe cases by the method elaborated by Haldane and himself, and found the total quantity sometimes increased and at other times decreased. Those with large volume seem to be in a worse condition than those with normal volume, an observation that coincides with the results obtained by Houston in studying edema as a symptom of anemia.—ED.]

In mild cases the **color of the blood** appears quite normal, in moderately severe it is pale red, later resembles watery meat extract, and in some extreme cases is almost colorless. Sometimes at the moment of issue the blood-drop loses its homogeneity when the yellowish or pale-reddish corpuscles are seen rolled into fine threads or small masses in the almost colorless fluid. The writers have never observed, as Fürbringer reports in severe cases (though it is true only exceptionally), a very dark even tar-colored blood. Gusserow mentions that in one of his cases after a transfusion of defibrinated blood the blood spurting from a small artery resembled thin coffee. This recalls so much the appearance of the blood in severe hemoglobinemic processes that we must assume that there was a hemolysis, and this in these cases does not belong to the simple picture of progressive pernicious anemia.

The coloring-matter of the blood is almost always strikingly diminished to even the simplest tests. True, there are pronounced cases in which the **percentage of hemoglobin** amounts to more than 50. The writer saw, for instance, a short time ago, a case manifesting marked morphologic alterations and severe general symptoms with a hemoglobin per cent. of 65 to 70; though, as a rule, the percentage is much lower, even to under 10 (Schauman, Case 47).

The **number of blood-corpuscles** likewise shows a marked diminution. A decrease of one-half is seen in comparatively mild cases. A million to the c.mm. is frequent. [The range of counts of the red corpuscles found at the first examination by Cabot[1] was as follows:

[1] *A Guide to the Clinical Examination of the Blood*, 1904.

From	500,000 to 1,000,000	36 cases.
"	1,000,000 to 1,500,000	55 "
"	1,500,000 to 2,000,000	39 "
"	2,000,000 to 2,500,000	9 "
	Total	139 "

Other authors have recorded rather lower numbers. Much, of course, depends upon the stage at which the disease is first recognized. Of 38 cases, Schauman found 1 above 2,000,000; 26 between 1,000,000 and 2,000,000; and 11 below 1,000,000.—ED.] A case of Quincke's, in which only 143,000 to the c.mm. were found, has become celebrated. In this case it is worthy of remark that after seventy-four days the patient showed 1,234,000, and after the course of several months appeared to her physician as "stout and well nourished." [Hills[1] has reported a case in which the count was 155,280 a few days before death. It is of interest to note that the strength and endurance of cases of pernicious anemia is often strikingly out of proportion to the low count of red corpuscles.—ED.]

More important in the comprehension of progressive pernicious anemia than the percentage of hemoglobin and corpuscles is the relation between the two factors. This constitutes a typical characteristic which is likewise evident in the histologic examination.

In the discussion of simple chronic anemia we showed that the diminution of hemoglobin was comparatively greater than that of the blood-corpuscles (see p. 69); in other words, that in ordinary anemic conditions the red blood-corpuscles lose not only in number, but in individual value. Hayem's accurate analyses, on the contrary, demonstrate that in progressive pernicious anemia the number of red blood-corpuscles may be considerably diminished, while their individual value remains normal or even exceeds the normal. For instance, Hayem found in one case 415,000 erythrocytes, which, reckoned according to their percentage hemoglobin, corresponded to 559,000 (individual value = 1.34). Quincke, too, showed that the blood of pernicious anemia is characterized by an increased amount of coloring-matter in proportion to the number of corpuscles. The relation which the individual value of the corpuscles bears to the severity of the disease is best shown by a table of Hayem's that gives the estimations in one patient for several months. In the last weeks of the disease, as the strength decreased, the value of the individual corpuscles rose:

[1] *Boston Med. and Surg. Jour.*, 1898, p. 139.

Date.	Number of red blood-corpuscles.	Average value.	Value in terms of an equivalent number of normal red blood-corpuscles.
Jan. 4th	738,730	1.25	877,287
Jan. 16th	781,200	1.01	923,460
Jan. 19th	834,250	1.32	1,101,153
Jan. 23d	868,006	1.23	1,015,807
Feb. 2d	723,260	1.60	1,663,560
Feb. 7th	680,050	1.51	941,933
Feb. 25th	292,500	1.70	498,668
Mar. 1st	Exitus lethalis.		

Laache confirmed these observations in a large number of cases and first proposed the explanation which is to-day generally accepted and which solves satisfactorily the whole question. He demonstrated that the increase in the average value of the blood-corpuscles depends on the fact that in progressive pernicious anemia many red blood-corpuscles are larger than normal and contain more hemoglobin.

[Too much stress has been placed upon the high color-index by some writers. My own conclusions regarding this matter[1] were that while a color-index above the normal is the rule, exceptions occur, but in such exceptional cases the index is still much above that seen in severe types of secondary anemias. Ewing[2] expresses a similar view, and Cabot[3] found the hemoglobin "relatively high" in 98 cases and "not relatively high" in 41 cases at the first examination. Strauss and Rohnstein[4] found indices varying from 0.50 to 1.95 and Cobbs in 36 cases found an average index of 1.0.—ED.]

The average diameter of the normal red blood-corpuscle is about 8.5 μ, and a diameter of 9.0 may be described as the high limit of normal. Larger cells, which we designate as *macro, megalo,* or *gigantocytes,* frequently occur in the blood of progressive pernicious anemia, so that the average diameter increases to 11–13 μ, and single examples are found of 16–18 μ (Askanazy).

Apart from size, the megalocytes are not particularly different from the normal red blood-corpuscles. As a rule, the concavity is less evident and is sometimes completely unrecognizable. The whole disc, as a consequence, appears regularly round, and "pessary forms" or even transitions toward such forms are scarcely ever found. The alterations in circumference are likewise more rare and not so pronounced. In fresh preparations the megalocytes show a normal hemoglobin color, in stained preparations an overstaining with eosin or orange G. In many cases a polychromasia is evident.

[1] "Diseases of the Blood" *Twentieth Century Practice of Medicine.*

[2] *Clinical Pathology of the Blood,* 1903.

[3] *A Guide to the Clinical Examination of the Blood,* 5th ed., 1904.

[4] *Die Blutzusammensetzung bei den Verschied. Anämien,* Berlin, 1901.

Still these large forms are not the only ones seen in progressive pernicious anemia; on the contrary, we also find erythrocytes, the diameter of which is normal or smaller than normal. The small and very small forms (microcytes) occur in similar numbers and are of the same size as in simple chronic anemia of like severity. The blood of the individual cases of progressive pernicious anemia receives its characteristic stamp from the number (percentage) of macrocytes and gigantocytes among all the red blood-corpuscles. This percentage signifies more than the average diameter of all the blood-corpuscles, since the latter is influenced by the number and size of the microcytes, so that, for instance, a markedly abnormal blood, as far as the proportion of large cells was concerned, might show a normal average diameter on account of the occurrence of a similar number of equally small cells.

Several examples will illustrate this. We found:

1. With advanced disease, bad general condition:
   In eight cases 71, 71, 66, 65, 60, 58, 57, 56 per cent. megalocytes.
2. With evident improvement of the general condition:
   In five cases 50, 48, 42, 39, 33 per cent. megalocytes.
3. On complete remission:
   In five cases 14, 14, 9, 3 per cent. of megalocytes.

It must be noted that the distribution of the large, normal, and small blood-corpuscles in the same preparation is often such that whole fields show only one kind. Hasty examination, therefore, can lead to considerable error in regard to the condition of the blood. Consequently the estimations should be made only on dried preparations faultlessly spread.

[Ewing states that "It may be said that unless 33 per cent. of the corpuscles are distinctly oversized the diagnosis of pernicious anemia should be made with reserve."—ED.]

By comparative examinations Laache determined that the disproportion in the quantity of hemoglobin accurately corresponds to the number of enlarged blood-discs. As long as the quantity of hemoglobin in the blood exceeded in comparison the number of corpuscles, the large discs were numerous, and as the quantity of hemoglobin approached the normal, they became scanty or disappeared. Laache explained the origin of the large forms as a sort of compensation on the part of the organism which endeavors to make up for the dangerous loss of oxygen-carriers by increasing their amount of hemoglobin, though he himself acknowledges that this explanation is scarcely satisfactory. A clearer light is thrown on this question by the work of

Ehrlich, who explains their origin in progressive pernicious anemia by a megaloblastic degeneration of the bone-marrow.

While referring for the theoretic consideration of megaloblasts and the necessity and possibility of their separation from the normoblasts, etc., to the explanations given on pp. 51–61, I shall add a few facts in regard to the occurrence of megaloblasts in the circulating blood. (For the prognostic and diagnostic significance of these cells, see the corresponding sections.)

The number of megaloblasts in the blood in progressive pernicious anemia is almost always very small, and, as insisted on previously, the absence of megaloblasts should not be considered in the diagnosis till one or several preparations have been entirely gone over, if possible, with the help of the mechanical stage. Accurate figures as to their relative numbers can not, therefore, be given, but we must content ourselves with statements such as, in the whole preparation, six, eight, etc., megaloblasts. Only in extremely rare cases, and then usually shortly before death, do they occur in such numbers that almost every field shows one or several, and in these cases they constitute an ominous symptom.

On account of the usual small number of megaloblasts, it is not surprising when, for instance, in two preparations made at the same time, several examples are found in one, none in the other. This shows that the negative finding must be employed with much greater caution in the diagnosis of a case than the positive. Moreover, evident fluctuations in the number of megaloblasts occur from day to day, without corresponding symptoms in the general course of the disease being recognizable.

It must not be forgotten that the presence of numerous megaloblasts in the bone-marrow by no means necessitates their occurrence in the circulating blood. No more than under physiologic conditions do the normoblasts pass over from their breeding-place into the circulation. What the irritants are that are capable of sending the megaloblasts into the blood-stream we do not know.

While there is no absolute correspondence between the occurrence of megaloblasts in the blood and the general course of the disease, experience teaches that they usually wander into the blood in the greatest numbers in the last days ante mortem. Moreover, though they may be absent for months at a time during remissions they usually appear again on the recurrence of the symptoms.

Sometimes, in addition to the megaloblasts, *normoblasts* are found, especially in the relatively mild cases. It appears to us remarkable

that Schauman found in all of his cases of bothriocephalus anemia both varieties of erythroblasts occurring together. From our personal experience, though it includes no bothriocephalus anemia, we must consider their simultaneous occurrence as a rarity. [Other observers are quite uniformly at variance with this view. As an illustration of the usual findings the figures of Cabot may be quoted here. Among 139 cases he found megaloblasts *predominating* in 109; predominating in later examinations in 27; no megaloblasts in 3. In other words, there were always some normoblasts associated with megaloblasts when the latter were found. This coincides with the editor's experience.—Ed.] The writers have not been able to discover that the occurrence of normoblasts introduced any change in the general disease-picture as it does in acute post-hemorrhagic anemia. Nevertheless, Askanazy reports a striking observation in this regard. In one of his cases of bothriocephalus anemia the blood showed a very large number of megaloblasts (40 to 50 on every cover-glass) and only isolated normoblasts. A short time after the removal of the tapeworm an exactly opposite condition was found, namely, a marked decrease in the megaloblasts, and a week later an evident increase in the normoblasts. Within three weeks the blood gradually returned to normal. In this case a pronounced general improvement accompanied the appearance of the normoblasts. The number of blood-corpuscles, which before the removal of the worm amounted to 1,200,000, rose in two weeks to 2,140,000, in four weeks to 4,250,000. The increase in blood-corpuscles was therefore introduced by the appearance of the normoblasts just as in acute post-hemorrhagic anemia. A case of kryptogenetic progressive pernicious anemia, described by Dorn, is even more pronounced. While showing the signs of a marked anemia the blood was suddenly inundated with normoblasts, which disappeared again in a few days. Within two weeks after this the number of red blood-corpuscles had increased three times. This is a condition well worthy of the name "blood crisis," suggested by v. Noorden for a similar condition in acute post-hemorrhagic anemia.

As pointed out first by Luzet, and since then by every observer who has had the opportunity of examining the blood of pernicious anemia in stained preparations, karyokinitic figures in every stage of development may be found, especially in the severe cases, though Schauman saw them in 1 case which later recovered. [Interesting papers on mitoses in the circulating blood have been recently published by Dock[1] and

[1] *Trans. Assoc. of American Phys.*, Nov., 1902.

C. Y. White.[1] The occurrence of such cells does not offer any important criteria for diagnosis or prognosis.—Ed.]

Before leaving this subject other peculiar changes of the red blood-corpuscles must be mentioned, namely, the occurrence of *punctate, granular*, or *larger deposits* in their protoplasm invisible in the fresh blood, but brought out by staining with methylene-blue. In preparations stained with Chenzinsky's fluid, for instance, these deposits are sometimes so fine and so closely packed together that the whole cell appears to be stained a homogeneous blue, and the structure can be recognized only with considerable difficulty. In other cases the granules are larger; again, some may be very fine, others large and rough. Moreover, they may be regularly distributed throughout the whole cell or be limited to a portion of it (see Plate II., Fig. 5).

As far as the writers have studied the literature, these cells were first mentioned in a dissertation prepared under v. Noorden's direction. In 1893 Askanazy described them in a case of anemia, and considered the granules as products of a karyorrhexis. In a monograph published in 1894 Schauman also mentioned these cells. In 1896 one of us was able to report more than 20 cases of progressive pernicious anemia in which they were unexceptionally found. Since then they have been frequently mentioned and described (Klein, Zeoni, Lenoble). A short time ago A. Plehn demonstrated morphologically similar elements in numerous cases of malaria and persons who dwelt in malarial districts. E. Grawitz has very recently confirmed Plehn's finding in several cases and demonstrated them also in progressive pernicious anemia due to carcinoma, suppuration, and leukemia. Finally it must be mentioned that Pappenheim and C. S. Engel have described similar deposits in embryonal red blood-corpuscles.

These cells are readily found in severe stages of progressive pernicious anemia after attention is once directed to them. Sometimes only one example in several fields, but frequently eight to ten examples in every field. Their frequency undoubtedly corresponds to a certain extent to the severity of the disease. When the severe stage of progressive pernicious anemia remits, they become more rare and gradually disappear entirely from the blood. [Stengel, White, and Pepper[2] found granular erythrocytes in 7 cases of pernicious anemia, and regard them as practically constant in advanced stages of this disease, though not as striking a feature in it as in lead-poisoning. The nature of these granules has been discussed in a previous section (see p. 59).—Ed.]

[1] *Univ. of Penna. Med. Bull.*, 1903.

[2] *Amer. Jour. Med. Sci.*, May, 1902.

EXPLANATION OF PLATE II.

FIG. 3.—PREPARATION FROM AN ADVANCED CASE OF PROGRESSIVE PERNICIOUS ANEMIA FROM UNKNOWN CAUSE.

a, Megalo- or gigantoblasts: the protoplasm shows marked polychromasia; *b*, stained granules in erythrocytes with normally stained protoplasm; *c* and *d*, polychromatophylic degeneration; *e*, megalocytes; *f*, normocytes.

FIG. 4.—PREPARATION FROM THE SAME CASE TAKEN SOME TIME LATER WHILE THE PATIENT WAS SUBJECTIVELY AND OBJECTIVELY IN PERFECT HEALTH.

a, Punctate erythrocytes with normal and anemic degenerated protoplasm; *b*, polynuclear leukocyte; *c*, normal red blood-corpuscles; *d*, somewhat enlarged erythrocytes.

FIG. 5.—SERIES OF CELLS FROM A CASE OF SEVERE PROGRESSIVE PERNICIOUS ANEMIA OF UNKNOWN ETIOLOGY; PREPARATION MADE TWO DAYS ANTE MORTEM.

a, Nucleated red blood-corpuscles characterized as normoblasts by the intense staining of the nuclei. *a′* and *a″*, karyokinetic figures in erythrocytes; the protoplasm finely punctate; *b*, beginning karyolysis in a megaloblast; *c*, erythroblasts with coarse granulation of the protoplasm; *d*, nuclear remains (?) and fine granulation of the protoplasm; *e* and *f*, finely punctate red blood-corpuscles; *g*, megalocyte with two blue nuclei; nuclear remains (?) in the polychrome protoplasm.

PLATE II.

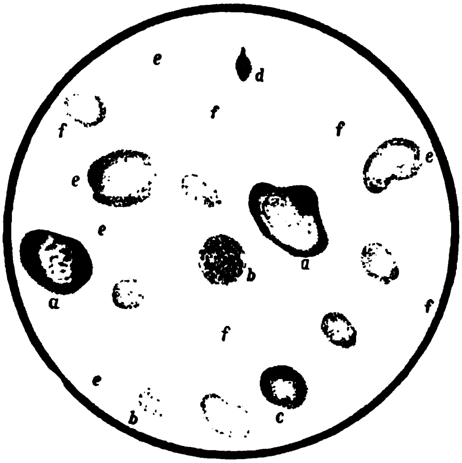

Fig. 3.

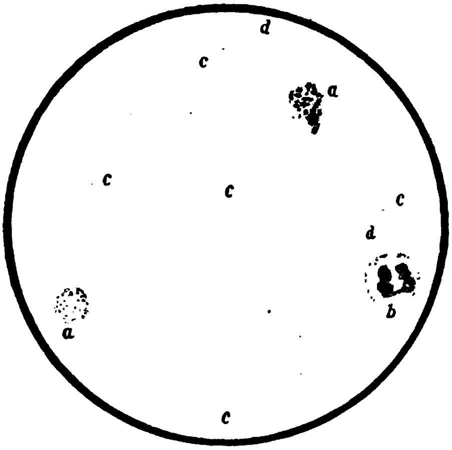

Fig. 4.

Fig. 5.

The significance of these granules is by no means assured. The writer will only mention that Plehn regards them as germs of the malarial parasite and designates them "karyochromatophilic granules." To consider them as an expression of polychromatophilic degeneration is not practicable, since, though they are often found in polychromatophilic degenerated cells, they occur not less frequently in those with normal stained protoplasm. The theory that they are products of nuclear destruction within the blood-corpuscles is supported by their occurrence in embryonal cells. Moreover, the series of pictures which the writer has obtained from one single preparation of progressive pernicious anemia (Plate II., Fig. 5), seems to him to confirm it. Still, the figures a' and a'', in which the cells show a mitotic figure, though the protoplasm is filled with the granules, are directly against this theory of karyorrhexis, since it would be necessary to assume the improbable explanation that the cells contained primarily two nuclei, one of which was destroyed, while the other went on to division.

Further observations on these cells which are of undoubted significance in the study of anemia are desirable so as to complete and explain our present knowledge. In order to avoid a misnomer on account of not understanding their significance and so put nothing in the way of their future designation, the writer will call them simply "punctate erythrocytes."

The further changes observed in the red blood-corpuscles in progressive pernicious anemia are not peculiar to this disease, but are more or less evidently pronounced in every severe anemia. Among these may be mentioned small erythrocytes and manifold alterations in shape, appearances which for a long time were regarded as characteristics of progressive pernicious anemia. It is to be added that in some cases the blood-corpuscles show very little change in shape in spite of a pronounced microcytosis; and, again, it sometimes happens that microcytes are entirely absent. In the very great majority of cases, however, the number of *microcytes* and poikilocytes is marked. Moreover, the ameboid movement of the poikilocytes ("pseudoparasite," Hayem) is not regularly seen, and when it occurs it can not be differentiated from that of other severe anemias.

Anemic or *polychromatophilic degeneration* is encountered in a large porportion of all the erythrocytes, and reaches higher grades than in any other disease. On staining with eosin-methylene-blue we not rarely find cells of such a pronounced blue color that they are recognized as erythrocytes only by their shape and the absence of a nucleus. The proof brought forward by C. S. Engel from his investigations of

embryonal blood, that polychromasia of the erythroblasts is not always a symptom of degeneration, but may be a physiologic peculiarity of a definite earlier stage of development, terminated the long-continued dispute between Ehrlich and Gabritschewsky in favor of the latter. In the discussion of Engel's discourse Ehrlich himself acknowledged a physiologic polychromasia in embryonal blood, though without dismissing its importance as a symptom of degeneration in the blood of adults (see p. 48).

The absence of rouleaux formation, to which some authorities attribute special significance, must be mentioned. It is more pronounced the smaller the number of red blood-corpuscles.

In the hematologic investigations devoted to progressive pernicious anemia during late years, the **white blood-corpuscles** have been treated in a somewhat off-hand fashion, and we find in the literature so far no special observations corresponding to our present-day demands. Still it is generally conceded that in the majority of cases their absolute number is decreased, and that any hyperleukocytosis must be attributed to a complication or a special phenomenon in the course of the disease.

The absolute number of leukocytes per c.mm. is in comparison with the normal (7000 to 10,000), invariably decreased. The lowest number, 1500 to 2000, was noted by Hayem. [Cabot's figures are as follows:

Leukocytes (when case was first examined).

Under 1000	11	cases
1000 to 3000	29	"
3000 to 5000	53	"
5000 to 7000	28	"
7000 to 10000	14	"
10000 to 13000	4	"
Total	139	—ED.]

The writers have made absolute estimations indirectly by comparing the number of red blood-corpuscles with the actual proportion of whites, and comparing the relation of the individual varieties of whites with one another. In progressive pernicious anemia these estimations require especial patience and time, since frequently several dried preparations must be entirely gone over with the help of the mechanical stage before a sufficient number of leukocytes is brought to view. We may introduce here figures from uncomplicated cases of kryptogenetic pernicious anemia taken at the height of the disease and at the beginning of the remissions.

Case 1. Sch. Oct. 25, 1894. Moderately bad general condition. Blood examination: Megalocytes, 66 per cent, ; in one cover-glass preparation, 8 megaloblasts. Poikilocytosis of moderate degree. Very many

punctate erythrocytes; marked polychromasia. Number of red blood-corpuscles, 1,340,000.

Estimation of the leukocytes: Proportion of white to red blood-corpuscles $\frac{W}{R} = 1:1275$.

In a differential count of 200 leukocytes we found:

Lymphocytes	50.0 per cent.
Polynuclear neutrophiles	42.5 "
Large mononuclear	0.5 "
Myelocytes	0.5 "
Eosinophiles	6.0 "
Mast-cells	0.0 "

November 12, 1894. General condition much improved. Blood examination: Megalocytes, 33 per cent.; no erythroblasts. Punctate erythrocytes scanty, about 10 in the whole preparation, Moderate polychromasia. Slight poikilocytosis. Number of red blood-corpuscles, 4,115,000.

$\frac{W}{R} = 1:218$. Differential count of 400 leukocytes showed:

Lymphocytes	12.0 per cent.
Polynuclear neutrophiles	78.2 "
Eosinophiles	9.5 "
Large mononuclear, Myelocytes, Mast-cells	0.0 "

Case 2. M—r. Oct. 15, 1894. Bad general condition. Blood examination: Megalocytes 71 per cent,; 8 megaloblasts in the whole preparation. Very marked poikilocytosis; considerable anemic degeneration; in about every second field a punctate erythrocyte. Number of red blood-corpuscles, 549,000.

$\frac{W}{R} = 1:1670$. Among 200 leukocytes were:

Lymphocytes	62.0 per cent.
Polynuclear neutrophiles	35.0 "
Large mononuclear	2.5 "
Eosinophiles	0.5 "
Myelocytes, Mast-cells	0.0 "

Oct. 31, 1894. Clinically much improved. Blood examination: Macrocytes, 39 per cent.; several normoblasts to a preparation, no megaloblasts. Punctate erythrocytes moderately numerous. Slight poikilocytosis and polychromasia.

Number of red blood-corpuscles, 1,525,000.

$\frac{W}{R} = 1:625$. Among 300 leukocytes were:

Lymphocytes	31.5 per cent.
Polynuclear neutrophiles	56.0 "
Eosinophiles	11.0 "
Myelocytes	0.5 "
Large mononuclear	0.5 "
Mast-cells	0.0 "

Case 3. S—r. Nov. 26, 1897. Moderately poor general condition. Blood examination: Macrocytes, 71 per cent.; 12 megaloblasts to a preparation. Marked poikilocytosis, polychromasia. Very many punctate erythrocytes (6–8 to a field).

(In this case the red blood-corpuscles were not counted.)

$\frac{W}{R} = 1:1120$. Among 308 leukocytes were:

Lymphocytes	44.5 per cent.
Polynuclear neutrophiles	49.5 "
Eosinophiles	5.0 "
Large mononuclear	1.3 "
Myelocytes	2 examples.
Mast-cells	1 example.

Dec. 9, 1897. Evident improvement in the general condition. Blood examination: Megalocytes 33 per cent.; no erythroblasts. Slight polychromasia, punctation, and poikilocytosis.

$\frac{W}{R} = 1:800$. Among 200 leukocytes were:

Lymphocytes	31.5 per cent.
Polynuclear neutrophiles	64.0 "
Eosinophiles	6.5 "
Large mononuclear	2.5 "
Myelocytes	0.5 "
Mast-cells	0.0 "

March, 6, 1898. Objectively and subjectively the general condition was excellent; the patient gave the impression of perfect health. Blood examination: Red blood-corpuscles of normal size with only slight alterations in shape. No erythroblasts. Several punctate erythrocytes in the preparation (in one 3, another 5). Slight polychromasia.

$\frac{W}{R} = 1:650$. Among 255 leukocytes were:

Lymphocytes	29.0 per cent.
Polynuclear neutrophiles	64.2 "
Eosinophiles	5.9 "
Large mononuclear	0.8 "
Myelocytes	0.0 "
Mast-cells (2 examples)	0.8 "

These cases which we have introduced only as examples of many similar ones permit us to draw the following conclusions in regard to the behavior of the white blood-corpuscles in progressive pernicious anemia:

1. The lymph-cells show an evident regular increase, reaching in one case 62 per cent. This increase in lymph-cells is assuredly not absolute but relative, and is due to the cells of the bone-marrow group being diminished. [An absolute increase in the number of lymphocytes is not infrequent, especially toward the end of the disease. Stengel[1] states that when preagonal leukocytosis occurred he found an excess of lym-

[1] *Twentieth Cent. Practice*, vol. vii.

phocytes ; Da Costa (*Clinical Hematology*) records similar observations, as does also Cabot (*Clinical Examinations of the Blood*). Strauss and Rohnstein[1] report a diminution in the multinuclear cells in pernicious anemia, the average being 52.5. The mononuclear cells at the same time rose to 45.1 per cent. in the 23 cases examined; 37 per cent. were lymphocytes, and all of the cases except one, in which the patient was *inarticulo,* the percentage of multinuclear cells was below 70 per cent. These results differ from those of McCrae, who found in 30 cases an average of 64 per cent. multinuclear and 34 per cent. mononuclear. The average of the lymphocytes in 11 fatal cases was only 29 per cent., while in 19 cases that improved under treatment the average was 31 per cent. Lymphocyte counts similar to those of Strauss and Rohnstein have been reported by Pepper and Stengel,[2] Klebs, Hayem, and others.—ED.]

2. The behavior of the *eosinophiles* is not satisfactorily explained in these cases, since their percentage was normal in several cases in which the other bone-marrow cells were considerably below the normal. Still, we must realize how readily accident may be responsible for differences in such small numbers (4 per cent.).

3. The diminution of the *polynuclear neutrophiles* is striking and is due to an absolute decrease, the result of the severe depression of the bone-marrow function.

In several cases (v. Noorden, Dorn) an extremely marked *hyperleukocytosis* was found, which on first glance gave the impression of a leukemia on account of the simultaneous occurrence of normoblasts. As has been mentioned in another connection above, this process was the forerunner of an extremely rapid improvement. In other cases, however, the occurrence of numerous leukocytes is a very ominous prognostic symptom, since it either indicates the existence of a complication—*e. g.*, a pneumonia or a suppurative process—or is the forerunner of death. For instance, a considerable hyperleukocytosis was found in 2 cases of Litten's within a few hours of death, and Gottlieb observed 1 case of genuine progressive pernicious anemia in which at the beginning no increase of white blood-corpuscles was found, while shortly before death they amounted to 30,000 per c.mm., making a relation of whites to red of 1 : 18.

In none of the writers' cases have they been able to find **morphologic alterations in the leukocytes** except once, the filamentous appearance of the lymphocytes described on p. 46. Gumprecht

[1] *Die Blutzusammensetzung bei den Verschied enen Anaemien*, Berlin, 1901.
[2] *Congress für Innere Med.*, Bd. 14.

describes several cases of degeneration of the lymphocytes, consisting in achromatism, enlargement and vacuolization of the nucleus, and breaking up of the protoplasm. Hayem observed in all very severe anemias an extraordinary increase of neutrophile granulations at the periphery of the polynuclear leukocytes, the half of these cells being thus altered. The same investigator makes the conjecture that the protoplasm of these cells imbibes hemoglobin in the severe cases. [Pase[1] has reported a case in which the neutrophile granules were absent from the polymorphonuclear cells. There was also an absence of basophile and eosinophile granules.—Ed.]

The other physical and chemic methods of investigation have so far shown no peculiarity of the blood in progressive pernicious anemia which would differentiate it from other anemic conditions of similar severity.

The **specific gravity** of the entire blood is, according to Lyonnet's statistics, invariably low in progressive pernicious anemia. The lowest specific gravity mentioned by him is 1027 in a case observed by Copemann. In cases in which Lyonnet made estimations over a long period, the specific gravity corresponded to the general condition.

The estimation of the **dry residue** of the blood was undertaken in several cases by v. Jaksch and Grawitz. Their lowest amounts were 10.82 and 9.07 per cent., respectively. The **percentage of albumin,** which v. Jaksch found decreased in one of his cases to 9.94 (normal 22.62 per cent.), corresponds to this. Still while in simple anemias this diminution of the percentage of albumin in the blood corresponds to a decrease of the same in the red blood-corpuscles, v. Jaksch found in pernicious anemia an augmentation of the percentage of albumin in the red blood-corpuscular substance ("hyperalbuminemia rubra"). This authority states the normal percentage in 100 gm. of moist red blood-corpuscles to be 5.52 N = 34.5 albumin, while in a case of progressive pernicious anemia N = 6.48, A = 40.5. The decrease of albumin and nitrogen in the whole blood is, therefore, attributable to the oligocythemia, since the erythrocytes present contain more albumin than normal. This finding is in accord with macrocyte formation and Hayem's increased percentage albumin in the individual blood-corpuscles.

Special investigations of the **serum** by Hammerschlag, Grawitz, and Dieballa show that even in severe cases of progressive pernicious anemia the blood-serum loses either not at all or only slightly in albumin. In one severe case (red blood-corpuscles 536,000, hemoglobin 20 per cent., specific gravity 1028.5), for instance, Dieballa found the percentage albumin of the serum to be 9.49 (normal 10 to 10.5 per

[1] *Riforma Med.*, 1899, p. 103.

cent.), while the percentage albumin in the entire blood was only the half of normal. Grawitz observed in similar cases the dry residue of the entire blood reduced one-half, that of the serum only about one-fifth.

The writers wish to state expressly that on careful manipulation of the blood the serum remains unstained, and that the occurrence of hemoglobin in the serum in progressive pernicious anemia, though frequently asserted, has not been proved. Positive investigations in regard to the resistance of the red blood-corpuscles in progressive pernicious anemia have, as far as the writers know, not been made, yet *a priori* we can assume that it is decreased, so that on glass the blood-corpuscles are readily broken up and the hemoglobin goes over into the serum if there is lack of care in the manipulation.

A very interesting property of the serum in progressive pernicious anemia has been recently observed by Maragliano. He found that the serum in certain pathologic conditions, among them progressive pernicious anemia in all its stages, dissolves on glass the healthy corpuscles and breaks up the hemoglobin, while the serum of healthy individuals, on the contrary, preserves the cells. According to Maragliano's investigations, this pathologic serum contains less salts than normal and its globucidal power can be destroyed even intra corpus by the intravenous injection of common salt. The clinical study of this remarkable phenomenon is limited on account of the lack of material, especially in the case of progressive pernicious anemia, still, if confirmed by further observations, it may be found serviceable in explaining the pathogenesis and the nature of anemias. That considerable biologic significance is attributable to it is shown by the recent work of Ehrlich on "hemolysins" and similar substances, which seem about to pave the way for a new mode of serum analysis.

Hayem and his pupils claim that the **coagulability** of the blood in progressive pernicious anemia is normal, while it strikes the writer, and Grawitz makes a similar observation, that in the majority of cases the small finger-prick bleeds a very long time, provided the amount of blood issuing from the wound was not originally too small.

Considerable importance in relation to the diagnosis and the conception of the nature of the disease is given by Hayem and Lenoble to the phenomenon discovered by the former, namely, that in different pathologic conditions the venesected blood does not separate into serum and coagulum. In a case reported by Lenoble there was not the slightest separation even after seventy-two hours. These two authorities regard this

phenomenon as of higher diagnostic importance than all the morphologic differences.

According to Hayem, in the same conditions in which this unconfirmed phenomenon occurs (therefore in progressive pernicious anemia), a diminution of the blood-platelets, which is often considerable, is regularly found. Van Emden found 64,000 and 32,000 per c.mm.; in other words, only the twentieth part of normal or less than this.

CLINICAL ALTERATIONS IN THE GENERAL CONDITION AND IN THE INDIVIDUAL ORGANS.

Among the **subjective symptoms** general weakness is most tormenting. The loss of muscular power forces the patient, even when the disease is only moderately severe, to an extreme restriction of exercise and to absolute rest for the greater part of the day.

[On the other hand, the strength of some patients is extraordinary, even to a late period of the disease. The editor observed one case in a man who was able to continue an unusually laborious occupation when his blood-count was reduced to 1,000,000 and the hemaglobin to 22 per cent.; even more striking instances than this are reported in the literature.—ED.]

Certain symptoms are aroused or increased by muscular effort, for instance, vertigo, palpitation, dyspnea, and cardiac oppression. Painful sensations occur in the region of the digestive tract, either spontaneously or after taking food. As in chlorosis, a dull sensitiveness of the bones, especially the tibia and sternum, is frequently present; percussion of these bones then produces severe pain.

Obedience to the demand for rest is often opposed by a marked degree of sleeplessness continuing for weeks. This is produced in part by other disturbances, for instance, of the heart. This sleeplessness is extremely difficult to combat, and forces us sometimes to the employment of morphin, in spite of the fact that in all cases of this kind narcotics should be prescribed with the greatest caution.

The pallor of the **skin** and of the visible mucous membranes is marked even in the early stages, and is of a quite peculiar tint, which is only incompletely characterized by the general designation "wax-like, death-like." Still this peculiarity is described with difficulty, since words are lacking to express the fine shades by which the ashen yellow of Biermer's disease is differentiated from severe chlorosis or advanced cachexia. That these indefinite though still evidently pronounced differences exist is shown by the fact that anyone who has seen several typical cases of progressive pernicious anemia is sometimes able to

make a diagnosis on the first glance, which further investigation confirms. In addition to the intensity and the peculiar character of the pallor, the majority of cases show a puffiness of the face, especially of the under eyelids, together with an indescribable languid expression of countenance.

Every trace of redness often disappears from the conjunctiva and the lips in outspoken cases. Rarely an evident icterus, though not marked, is observed in the skin and conjunctiva (Quincke).

The skin is ordinarily dry, yet profuse outbreaks of perspiration are readily produced by slight influences, emotional excitement, insignificant bodily efforts, etc.

A symptom which is practically never wanting is edema, especially of the legs and of the under eyelids, though it is also seen in other places on the body. The swelling is practically never marked, but is very persistent, and is noticeable as one of the earliest symptoms of the disease; moreover it readily occurs again in patients who otherwise show a complete remission. The comparatively slight grade of the edema and its independence of body position makes it probable that it is not due to stasis, but, as in other anemias, to the alterations in the blood-vessel walls described by Cohnheim.

[Thomas Houston[1] has made some investigation of the edema of anemic conditions and finds in the edema the cause of the retention of body weight of patients having pernicious anemia. A gain in body weight in pernicious anemia when unattended with increase of hemoglobin indicates dilution of the blood and escape of serum into the tissues. It is therefore an unfavorable sign.—ED.]

Small hemorrhages about the size of the head of a pin in the skin and mucous membrane of the mouth are among the most frequent symptoms. From the observations in the literature, large extravasations appear to be very rare.

In the diagnosis of some cases it is important to remember that Laache several times observed a dirty-yellowish pigmentation of the skin which recalled Addison's disease. The suprarenal capsules in these cases were normal. Immermann also reports 2 cases of progressive pernicious anemia in which an outspoken bronzing of the skin developed; in 1 which came to autopsy the suprarenal capsules were likewise found intact.

A peculiar and undoubtedly rare symptom has been reported by Eichhorst. He observed several cases in which the patients "disseminated to a considerable distance a very repulsive fecal, disgusting

[1] *Brit. Med. Jour.*, June 14, 1902.

cadaveric odor," which was evidently not the fetor ex ore described by several other writers. This symptom occurred usually in comatose patients two or three days before death. After death the odor was no longer apparent.

The **nutritive condition** of the patient remains good even after the disease has lasted many months, and in cases that prove fatal without complications the subcutaneous fat is still found well developed. Only when obstinate vomiting and diarrhea persist for a long time do we see marked loss in weight. Though in many cases the condition of nutrition is moderately good while the amount of nourishment taken is extremely small, this is due to the lowered metabolism on the part of the patient, who on account of exhaustion avoids every superfluous movement.

The observations on **metabolism** in progressive pernicious anemia correspond exactly with those made in other forms of anemia. These show that the *process of oxidization* is not different from that in health, in fact, according to Kraus, Thiele and Nehring, and others, it is slightly increased in comparison with the normal. How the organism accomplishes a normal oxygenation in spite of the marked absolute diminution in hemoglobin and red blood-corpuscles has been discussed previously.

Investigations on *albuminous decomposition* in progressive pernicious anemia were undertaken by H. Müller, Ferrand, Eichhorst and Quincke, and Laache, though they did not make estimations of the total urinary nitrogen, but of the urea. Their results are contradictory. Ferrand and Müller claimed a considerable diminution in the excretion of urea, while the others found what under normal circumstances would be a decided increase, and, considering the extremely lowered nourishment, must be designated as a striking increase. Quincke, for instance, found in 1 case an excretion of 44 gm. of urea in twenty-four hours. In general, periodic fluctuations were noticeable, and Laache states that the amount of urea increased especially during regeneration simultaneously with the new formation of blood-corpuscles. From estimations of the amount of nitrogen, Bohland found in 2 cases of severe ankylostoma anemia a very decided increase in albuminous decomposition, which he attributed not to the anemia, but to the effect of a specific worm toxin.

[Rosenqvist[1] has studied the metabolism in pernicious anemia. In 21 cases of bothriocephalus anemia and in 3 cases of cryptogenetic pernicious anemia metabolic investigations were made. Before the discharge of the parasite, he found in the majority of cases an increase in

[1] *Zeitschr. f. klin. Med.*, 1903, XLIX., 1, 2, 3, 4, p. 193.

albuminous destruction, but after the discharge of the worm an albuminous increase takes place. The nitrogen balance, however, remains positive, even when the parasite is present, and he believes, therefore, that the destruction of albumin is a periodic one. The same sort of periodic destruction and augmentation is observed in idiopathic pernicious anemia.—ED.]

In color, daily amount, specific gravity, and reaction, the **urine** shows no special peculiarities, the fluctuations in uncomplicated cases lying within the normal limits. Still, it must be noted that very often (according to Schauman), without exception, a pronounced indican reaction can be obtained, to which H. Müller called attention in his first publication. As a sign of increased urinary decomposition other bodies besides indican have been found in the urine by Hunter; for example, the so-called putrescin and cadaverin (tetra- and pentamethylendiamin).

Laache's observation of a *hematuria,* which must be considered a great rarity, is to be regarded as an associated symptom of the general hemorrhagic diathesis. In this connection we must expressly insist that a hemoglobinuria has never been seen in cases absolutely determined to be progressive pernicious anemia. The hemoglobinuria occurring after transfusion of blood has nothing to do with the disease.

An abnormally high percentage of *urobilin* has been demonstrated as a regular occurrence by several investigators.[1] That this must be regarded as a direct proof of an increased blood destruction has been stated in another section.

In a large number of cases a slight degree of *albuminuria* occurs which responds to one test and fails in the next on the same day. Since no signs of inflammation are found by the microscope, provided the cases are unassociated with complications, the simplest explanation for the albuminuria is to be sought in alterations of the kidney epithelium produced by the anemia. Laache, Birch-Hirschfeld, and others report that they observed in several cases throughout long periods *peptonuria* and *albumosuria* without a simultaneous albuminuria.

The occurrence of *sugar in the urine* has never been reported. In a recent work on alimentary glycosuria, Niepraschk studied the effect of the administration of grape-sugar subcutaneously and large amounts of cane-sugar per os in 1 case of progressive pernicious anemia. After the former he found a glycosuria in that of the 80 gm. of grape-sugar injected (about one-fourth was excreted), though after eating 87.5 gm. of cane-sugar no glycosuria occurred.

Laache found *leucin* practically constant in the urine of progressive

[1] Hunter, Mott, Grawitz, and others.

pernicious anemia. He found *tyrosin* in 3 cases, v. Noorden in 2 cases sub finem vitae, while other cases failed to reveal these substances.

Uric acid was found increased both absolutely and in comparison with the urea in one case by Quincke. The former figures were 1 : 11.5 gm. (normal 1 : 50 gm.), the latter 1.7 gm. (normal 0.5 : 1.0 gm.). This increase has been confirmed by other investigators in several cases, but it is by no means constant, since normal averages are also found.

The writer mentions the finding of *acetonuria* (v. Jaksch), *diaceturia* (v. Noorden), though he can not draw any conclusions from them.

In accordance with Ehrlich and Schauman, the writer has never been able to find the *diazo-reaction* in the urine.

In reference to the inorganic constituents of the urine, it must be mentioned that Damaskin often found the quantity of iron increased, which is probably attributable to the increased destruction of red blood-

Fig. 6.

corpuscles. The chlorids are excreted in amounts corresponding to the quantity of nourishment. The phosphates are enormously increased (v. Noorden).

Nothing of importance can be added to Biermer's original description in regard to the behavior of the **temperature.** It shows no constant relation to the severity of the disease or its individual stages. In a patient, for instance, whose temperature-curve is given, the improvement, which set in soon after her admission to the Moabit Hospital, progressed with a gradual diminution of the fever (see Temperature-curve I., Fig. 6). On the other hand, patients may show for many weeks, even months, a pretty severe condition without the

FIG. 7.

temperature-curve being distinguishable from that of health. In still other cases absolutely irregular fluctuations of temperature may be seen, and finally these differences in the temperature may periodically alternate with one another, as in Temperature-curve II., Fig. 7 (Laache).

Elevations of temperature to 40°, 40.5°, 40.8° (Eichhorst), as well as low degrees of temperature, especially as forerunners of coma or during coma, have been observed. For instance, H. Müller found in 1 case which showed a subnormal temperature during the last two days a temperature shortly before death of 25.8° in ano.

[Osler[1] found fever in three-fourths of his cases.—Ed.]

Schauman observed in 80.9 per cent. of his cases of bothriocephalus anemia elevations of temperature associated with the fluctuations described above. That the fever in bothriocephalus anemia stands in close relation to the disease-process, is evident from Schapiro's curve, which shows in its first part a completely irregular type of fever, while after the removal of the worm the temperature became normal in a few days.

No satisfactory explanation for the origin of the fever and its ever-changing behavior in progressive pernicious anemia has been given. Silbermann's hypothesis accords best with the facts, namely, that a ferment intoxication is produced by the increased destruction of blood-corpuscles, which in turn produces the fever. There are undoubtedly considerable differences in the pathogenesis of isolated cases, and we have sufficient grounds for the assumption that an increased destruction of blood-corpuscles does not take place in all cases by any means. It is possible that those cases in which it does not occur run their course without an elevation of temperature.

The alterations on the part of the **circulatory apparatus** have always attracted the greatest attention from clinicians. In the first place, we may mention subjective cardiac sensations consisting in violent palpitation and tormenting anxiety which rob the patient of sleep, induce severe dyspnea, and make him restless in his efforts to alleviate his distress by a change in position. In less severe cases these disturbances are not continuous, but are brought on by excitement, slight bodily effort, etc. Even in very mild cases a marked palpitation may appear in response to insignificant irritation, which is exceedingly tormenting and only gradually ceases.

Upon objective examination of severe cases we find a marked movement of the whole cardiac region in which the apex-beat is scarcely visible. On palpation, the apex-beat is more or less evidently apparent in its normal situation. Percussion shows, as a rule, normal cardiac dul-

[1] *The Principles and Practice of Medicine.*

ness, though sometimes as an expression of complicating hydropericardium there is a moderate enlargement toward the right. Auscultation discovers over all ostia an evident, sometimes soft, sometimes rough, blowing systolic murmur. The diastolic sound is almost always preserved (yet according to Biermer diastolic murmurs may occur without valvular disease being found post mortem). It is impossible in severe cases to decide on one examination whether an organic heart disease is present or whether the symptoms are to be attributed entirely to the anemia. The latter assumption would be naturally supported by a normal percussion-area and a regular rhythm, while organic disease would be indicated by a stormy heart action and intense murmurs. If fever simultaneously exists, the suspicion of an acute endocarditis may be aroused.

This description, which corresponds to the most advanced cases, is subject to every gradation. The murmurs especially may show alterations of intensity and differences in their location. They may be heard simultaneously over all ostia, or again over any one exclusively; even the diastolic murmur is, according to Eichhorst, very variable in its localization. That the marked accentuation of the second pulmonary tone is by no means an evidence of a valvular defect is shown by the further history of the cases and the postmortem reports. In individual cases the symptoms fluctuate considerably and often show decided variations within days or even hours, which is the best proof against organic disease.

No strict correspondence between the intensity of the anemia and the severity of the cardiac symptoms appears to exist. In Schauman's statistics of cases in which no cardiac murmurs were audible we find advanced cases with only 275,000 red blood-corpuscles. Yet when cardiac symptoms are found during the course of progressive pernicious anemia they increase or decrease, corresponding to the increase or decrease of the anemia.

It is not to be doubted that all these symptoms, the subjective disturbances as well as the dilatation and the murmurs, are attributable as a rule to the changes in the heart described in the section on Pathologic Anatomy. Still the great number of theories concerning this point demonstrate that the explanation of the connection between the two is not satisfactory. Moreover, it should be mentioned that Stricker and Rosenstein each described a case of progressive pernicious anemia in which, during life, systolic murmurs were heard over the heart, while after death no fatty degeneration of the cardiac muscle-fibers or disease of the valves was found. In such cases the heart-murmurs can apparently be attributed only to the altered composition of the blood.

In regard to the other portions of the circulatory apparatus, the functional murmurs which are frequently heard over the jugular veins on one or both sides must be mentioned; in other not less severe cases these murmurs are wanting.

Eichhorst and Schauman frequently observed active pulsation in the carotids, and heard in other peripheral arteries a clear, loud systolic sound.

The pulse in the radial artery shows in all cases a marked diminution of tension, and in different patients considerable variations in size. The frequency is invariably increased; it runs during rest between 90 and 100, is readily increased to 110 and 120 by slight irritation, and even during complete remission continues over 80. [Osler states that the pulse is full and strong and frequently suggests the water-hammer pulse. A capillary pulse is frequently noted.—ED.]

There is nothing to note in regard to special symptoms on the part of the **respiratory apparatus.** The dyspnea mentioned above is merely a result of the cardiac disturbances. In severe cases serous hemorrhagic transudates may be found in the diaphragmatic space. It is to be added that Schauman observed hemorrhagic fibrinous clots coughed up a few days ante mortem.

The **digestive tract,** on the contrary, plays a prominent rôle in the clinical picture as well as in the etiology and anatomy. In the first place, we may mention a serious *loss of appetite,* which in severe cases increases to an unconquerable distaste, even repugnance, for every form of nourishment and for individual dishes. The writer has several times observed patients who took their ordinary nourishment without appetite, but acquired an unconquerable distaste for meat, which up to that time they were fond of. They refused the smallest morsel for weeks at a time, no matter in what form it might be offered. In other severe cases the appetite remains undisturbed and boulimia has even been reported by several clinicians.

A symptom mentioned by several recent authorities consists in an exceeding *sensitiveness of the tongue* and the mucous membrane of the hard palate, the cheeks, and the gums. In one of the writers' cases this sensitiveness was shown especially in regard to vegetable acids, and wine, grapes, apples, etc., produced the most tormenting burning. On examination the writer found on the tip and back of the tongue and on the mucous membrane of the cheeks circumscribed reddish-brown mahogany-like discolorations, of punctate to dime size, which were undoubtedly the sites of hyperesthesia. It is very probable that these represented hemorrhages into the mucous membrane. In another

patient (a female) an intense painfulness of the tongue and the gums appeared as the first symptom of the disease, lasted three weeks, and disappeared under symptoms of marked salivation. Ewald observed in 1 case round vesicles the size of the head of a pin on the tip of the tongue, its internal surface, and on the mucous membrane of the lips and cheeks, which rapidly disappeared and left behind a surface desquamated of epithelium. He considers this process to be similar to the erythema bullosum described by O. Rosenthal.

A feeling of excoriation in the mouth and thoughout the whole length of the esophagus has been observed by H. Müller and Laache in several patients. Yet we must not forget that the persistent use of arsenic can produce the same symptoms.

Vomiting is very frequent. In severe cases it may become violent and uncontrollable, and then render the taking of nourishment almost impossible; in other cases it appears only after hearty meals. The vomit consists merely of food masses or greenish mucus. In 1 case of H. Müller's traces of blood were found in the vomit, and Barclay observed shortly before the death of a patient "dark masses in the vomit."

As in simple anemias, we find associated with the vomiting and independent of it intense *painfulness of the gastric region*, which is diffuse or circumscribed and manifests itself spontaneously or only on pressure. The abdomen is frequently somewhat distended, but soft and readily compressible. Pulsation of the epigastric region is frequent.

A *chemic investigation of the gastric juice* has been recently carried out with especial attention to the frequently associated atrophy of the gastric mucous membrane. Exact figures can not at present be given, yet in an exceedingly large proportion of cases there was a marked diminution of the gastric secretion, even to its complete absence ("achylia gastrica"). These investigations were made principally by Schauman and Martius. Of 11 patients of the former, 10 showed no free hydrochloric acid. [In a recent communication Einhorn[1] denies the asserted relationship of pernicious anemia and achylia gastrica. In these cases the gastric juice was present and even normal.—Ed.]

Moreover, Martius, in his frequently quoted monograph, showed that the achylia was not always attributable to atrophic conditions. In cases in which the absence of hydrochloric acid was determined a more or less extensive atrophy of the gastric mucous membrane was usually found post mortem, yet the finding of hydrochloric acid constituted no

[1] *Med. Record.* Feb. 28, 1903.

positive proof that the mucous membrane was uninjured, for 1 such case of Koch's showed a marked degree of atrophy.

Disturbances of intestinal activity are very frequent and vary in kind and degree. In one series of cases we see obstinate constipation, in another persistent diarrhea, and even an alternation of the two in the same patient, while still others manifest an absolutely normal digestion.

The appearance of the *feces* shows nothing out of the common. Isolated cases have been described (Wallenstein, quoted by Herz), in which the evacuation was markedly acholic, indicating, therefore, a considerable disturbance in fat resorption. On microscopic investigation, which should be frequently repeated in every case, the most important occasional finding is the eggs of the bothriocephalus or other intestinal worm. The discovery of leucin and tyrosin crystals, to which some significance was attributed at the beginning, is, according to Eichhorst, characteristic only for the diarrheal stools, and not for the progressive pernicious anemia. [A case reported by Jürgensen, in which "marked anemia" disappeared after administration of purges and the discharge of immense numbers of Bacterium termo, and the recent case of Pase,[1] in which the presence of large numbers of a long bacillus in the stools was a notable feature, may be recalled in this place. Hunter's recent claims regarding gastro-intestinal streptococcus infection may also be noted.—ED.]

The *absorptive activity of the intestine* can be determined from the general condition of the patient and the general composition of the stools. The comparatively good nutritive condition shows, as in other anemias, that severe disturbances of resorption are not characteristic of anemia; in fact, only disturbances of fat absorption, as previously mentioned, have so far been determined with certainty. [Bloch[2] has found that a considerable proportion (up to 20 per cent.) of the nitrogen of the food is passed in feces unused, because of insufficiency of the intestinal glands; but even with marked atrophy of the mucous membrane the absorption of food may be good.—ED.]

The increased quantity of decomposition-products in the urine points to abnormal decomposition of albumin in the intestine. [Bloch[3] has recently investigated the occurrence of indicanuria and finds this by no means a constant condition. When present it is due to interference with the bowel movements.—ED.]

On the part of the *peritoneum* no conspicuous clinical symptoms are apparent, though antemortem a slight grade of ascites may be found.

[1] *Riforma Med.*, 1899, p. 103. [2] *Deutsch. Archiv f. klin. Med.*, Bd. lxxvi.
[3] *Deutsch. Archiv f. klin. Med.*, Bd. lxxvii.

The *spleen* is almost always of normal size or somewhat smaller than normal. Slight enlargements, to the palpating finger, are sometimes found; in these cases (Eichhorst) the spleen is firm and insensitive to pressure. [In McCrae's series of 40 cases,[1] a palpable spleen was found in 6 cases, but the enlargement was never considerable.—Ed.]

Naturally with a special etiology for the progressive pernicious anemia, for instance, malaria, a large splenic tumor may be found without the necessity of making such a case an exception. Still, reports of cases with very large splenic tumors of unknown origin are not infrequent, especially in the older literature. As long as these reports are not completed by a very careful analysis of the blood, it is impossible to decide whether they are to be reckoned with progressive anemia or pseudoleukemia or some other group of diseases. The writer has had the opportunity several times of examining patients with severe anemia associated with considerable enlargement of the spleen, yet on a careful blood examination he has never obtained the characteristic picture of progressive pernicious anemia. [A case of typical pernicious anemia without malarial history has been under the editor's observation in several remissions, in each of which very considerable enlargement of the spleen was present. In one of Palmer Howard's cases (quoted by Osler, *Principles and Practice of Medicine*) the spleen weighed 1 lb. and 5 dr.—Ed.]

The **liver** is not rarely somewhat increased in size and tender on pressure.

The **lymph-glands** accessible to clinical examination are found no more enlarged than in many other diseases. [Pathologic conditions of the abdominal and other internal lymph-glands will be referred to later.—Ed.]

No peculiarities are to be reported on the part of the **sexual apparatus,** omitting the almost regular cessation of menstruation. Laache observed in 1 case the menses, which had failed for some months, appear again several weeks before death.

During the last fifteen years attention has been directed to the alterations in the central and peripheral **nervous system.** While referring to the alterations to be described in the anatomic section, the writer wishes to mention here the clinical peculiarties in order to show how far they correspond with the anatomic findings, and what relation they bear to the clinical course of the disease.

Manifold alterations are observed in the brain, the spinal cord, and the peripheral nerves.

[1] *Jour. Amer. Med. Assoc.*, Jan. 18, 1902.

The psychic behavior of the patient in certain severe cases shows how the **cerebral functions** are drawn into sympathy. Thus we sometimes find, for instance, contrary to the increased general irritability so frequently seen in all anemias, a stupid indifference to surroundings, to external impressions, and to the disease itself. The writer has observed such symptoms in a case which, as far as the physical condition was concerned, was still in a very early stage of pernicious anemia. According to the accounts of his relatives he had shown until shortly before not the slightest abnormality in his mental behavior. The first disease symptom which was remarked was that the patient, up to that time industrious, ceased work without giving any explanation and without defending himself from the reproaches made on account of his idleness. He bore without contradiction his transference to the hospital. Here he showed himself absolutely without concern and without will. On command he would perform any little task in the ward or in the kitchen, but if left to himself he spent the whole day without manifesting the slightest interest in his surroundings. His memory too seemed decidedly influenced. In 1875 Schule reported 3 cases with psychoses (melancholia, dementia). During life their pallor was striking, and on post mortem lesions corresponding to a progressive pernicious anemia were found.

In certain cases we see violent emotional, even maniacal, attacks, delirium, and hallucinations. These outbreaks are usually only transitory, and intermit with the previously mentioned apathy. Occasionally we see a comatose condition. This is usually a terminal symptom, though exceptionally the patient may awake from a pronounced coma and recover completely.

Numerous disturbances of a somatic nature due to actual disease of the cerebrum have been observed. A most important cerebral symptom, rigidity of the pupil, was described by Minnich in one of the first cases. Biermer, H. Müller, Laache, Nonne, and others report cases of progressive pernicious anemia in the course of which transient, slight pareses of one-half of the face, a transitory hemiplegia, paresthesias of different kinds, motor irritative symptoms of one-half the body, aphasic conditions, symptoms of vertigo, and weakness of memory occurred.

Disturbances of speech are not rare. For instance, the previously mentioned patient manifested a slow, yet indistinct, stammering speech, noticeable especially in connection with the well-known difficult test-words. This case, however, produced the impression that there was less an inability to form the words than a weakness of will.

The investigations on the alterations of the **spinal cord** are more numerous than significant. Since Leichtenstern in 1883 first described 2 cases manifesting tabetic symptoms, the neurologists have devoted special attention to these conditions so important in the pathology of progressive pernicious anemia. The primary observations on which the present conclusions are based are due particularly to the investigations of Lichtheim, Minnich, Eisenlohr, and Nonne. [Burr[1] has reported a series of cases with studies of the lesions.—Ed.]

The clinical symptoms of spinal disease described in connection with progressive pernicious anemia are manifold. In the first place, the general muscular weakness found in almost all forms of anemia may reach such a high grade in pernicious anemia that the limbs appear almost paralytic. It can scarcely be doubted that the disturbance of movement in these cases is not attributable entirely to the atrophy and degeneration of the muscles, but a disturbance of innervation must also be taken into consideration. Moreover, on account of the rarity and insignificance of peripheral nervous disturbances in pernicious anemia, these symptoms point to a participation of the spinal cord.

In a second group of cases are encountered disturbances of sensibility and motility which resemble more or less those ordinarily seen in tabes. In fact, the whole classic symptom-complex of tabes dorsalis may be present: Abolishment of the patellar reflex, rigidity of the pupil, pronounced ataxia, paralysis of the bladder and rectum, lancinating pains, anesthesias and paresthesias. Again, the disease-picture may deviate in individual symptoms from that of tabes, just as genuine locomotor ataxia itself does not always present the entire syndrome fully developed.

In contrast to the tabetic cases there are a few which present the clinical symptoms of spastic spinal paralysis, exhibiting spastic paresis of the extremities and increased patellar reflexes (Leyden, Eisenlohr, Brasch).

The cases imitating a pure form of tabes and spastic spinal paralysis constitute only the limits within which a number of disease-pictures arise with every variation of the clinical spinal symptoms. Transitions are not infrequently observed of such a nature that the reflexes primarily increased, are later abolished, or the reverse, namely, the disappearance of a Westphal's symptom after it has persisted for some time, and the return of a normal reflex irritability (Brasch).

[McCrae[2] found nervous symptoms in 27 per cent. of his series of 40 cases, and McPhaedran[3] records such symptoms in over 40 per cent.

[1] *University Med. Mag.*, 1895. [2] *Jour. Amer. Med. Assoc.*, Jan. 18, 1902. [3] *Lancet*, Jan. 18, 1902.

of his cases. The prevailing type in McCrae's cases was some sort of sensory disturbance, especially in the extremities, associated with a more or less spastic condition. Brown, Langdon, and Wolfstein[1] report 1 case of combined sclerosis of the Lichtheim-Putnam-Dana type; and Batten[2] 1 of subacute combined degeneration of the cord. Henry[3] records an instance of extensor palsy of the hands and feet evidently due to peripheral neuritis. He considers the possibility of arsenical neuritis in this case, but does not accept this explanation. The editor in commenting on Henry's case[4] holds a contrary view, and refers to cases of distinct arsenical neuritis and pigmentation corresponding exactly with Henry's case. It may be added that tingling, numbness, etc., are frequent symptoms in pernicious anemia and other diseases in which large doses of arsenic are administered. F. Billings[5] discusses the nervous symptoms of pernicious anemia. Of the 41 cases recently under his observation, paresthesia occurred in 40. In 27 cases there were subjective disturbances only. In 11 cases there was a spastic and usually also an ataxic condition which steadily increased. In 3 cases flaccid paraplegia with loss of knee-jerk and of control of the bladder and rectum eventually developed. Girdle sensation was present in all of the cases that developed spasticity. Billings believes that it is probable that these changes are produced by a toxin which tends in one case to produce hemolysis, in another case degeneration and sclerosis of tissue, while in the third case it causes both kinds of change. This toxin is most probably gastro-intestinal in origin. He does not believe there is any essential difference between the spinal sclerosis of pernicious anemia and that which occurs independently.—ED.]

No symptoms of importance are to be described in connection with the peripheral nerves. As results of the defective circulation, possibly also of the alterations in the spinal cord, may be mentioned paresthesias, like formication and rheumatic pains, particularly in the lower extremities. One of the writer's patients manifested for years severe migraine attacks, which ceased about the time when the progressive pernicious anemia began.

There is a marked inconformity between the anatomic alterations of the nervous system (described under their proper head) and the clinical symptoms. On section evident lesions may be found in the spinal cord without clinical symptoms during life (Nonne); and reversely severe functional disturbances may attract the attention of the clinician without

[1] *Jour. Amer. Med. Assoc.*, March 2, 1901. [2] *Lancet*, Jan. 19, 1901.
[3] *Amer. Jour. Med. Sci.*, Aug., 1900. [4] *Chicago Med. Recorder*, Jan., 1903.
[5] *Progressive Med.*, June, 1900.

the pathologist being able to discover an anatomic foundation (Goebel). It is to be assumed that on a further perfection of the methods the negative findings in the latter case will be narrowed down.

Both the functional and structural alterations in the central nervous system are characterized by the fact that they rapidly develop from small beginnings, and in comparison with ordinary tabes quickly prove fatal. The majority of cases run their course in six to twelve months, though, according to Dana, a duration of as much as three years sometimes occurs.

These are, in brief, the observations made by neurologists on the subject in hand. What conclusions can the student of anemia draw from these observations?

We must notice first that there is no regular correspondence between the clinical spinal symptoms and the anatomic spinal lesions, or between the latter and the anemia. On the one hand, we may observe a large number of cases of pernicious anemia for months without encountering any indication of a spinal disease even on careful examination; on the other hand, there are relatively mild cases of anemia in which cerebral and spinal symptoms are evidently pronounced (Leyden). In one group of cases (Leichtenstern) the spinal disease is observed first, the pernicious anemia becoming manifest later; in another, the anemic and nervous symptoms break out simultaneously; and finally, the latter may become apparent only after the anemia has existed some time (Minnich). From this irregular behavior the important conclusion suggested by the early writers (Nonne) seems evident, namely, that the spinal disease is not a result of the anemia any more than this is secondary to it, but that both are coördinate symptoms of the same process. This assumption is supported by 2 cases of bothriocephalus anemia reported by Lichtheim and Minnich, in which tabetic symptoms were observed during life and extensive degeneration of the posterior columns of the spinal cord were found post mortem. The toxic substances on which, according to our assumption (p. 235), the anemic action of the worm depends, apparently produced the spinal disease also. A similar assumption must be made in the cases of pernicious anemia in which the etiology is obscure. Therefore, since we have every ground for attributing the origin of pernicious anemia to toxic causes, and since the alterations described in the spinal cord are not specific to severe anemias, but show a close similarity with those occurring in a large number of cachectic and toxic conditions (Redlich, Dana), we can assume an intoxication of unknown origin and unknown nature as the cause of both the anemia and the spinal disease.

A marked similarity between the two conditions is shown by the fact that each manifests a particular tendency to remissions which are entirely independent of one another. Thus, Nonne reports a case in which the sluggish pupillary reaction became normal, the abolished patellar reflexes returned, the occasional disturbances of the bladder function and the ataxia retrogressed while the symptoms of the anemia advanced progressively to death. Reversely in 1 case of Eisenlohr's the anemia disappeared completely within several months after the removal of a Tenia mediocanellata, while the spinal disease showed no improvement. Bowmann, however, reports a case with a pronounced correspondence between the two symptom-groups. In this case, after the anemia had existed about three years and the spinal disease apparently about nine months, a simultaneous improvement of both set in under arsenic treatment and continued for more than six months. The relapse which occurred after a short time affected in the same way the blood-tissue and the spinal cord.

Still, whether the disappearance of the spinal symptoms is to be referred to an actual retrogression of the anatomic lesions in the spinal cord, is doubtful. Brasch's observation, at least, is against it. In this the return of the patellar reflex was attributable to new processes in the pyramidal tracts, which were added to the previous degenerations in the posterior columns. That the improvement of the general condition may affect the spinal symptoms favorably is natural, since there is a period at which the nerve-fibers are incapable of function without being entirely destroyed. If now favorable nutritive conditions arise, the fibers may recover their full functional capability. In special cases, therefore, we can conceive that a retrogression in the clinical spinal symptoms is attributable to the improvement in the anemia.

Among the alterations encountered in the **organs of special sense,** those of the *eye* are of the greatest importance. Subjective disturbances, such as flashes of light and dimness of vision, about which patients frequently complain, are seen in the early stages of the disease at a time when objective alterations in the eye can not be demonstrated. We may likewise mention again the pretty frequent occurrence of a more or less marked edema of the under eyelids.

As associated symptoms of the general inclination to hemorrhage we find occasionally effusions into the conjunctiva bulbi palpebrarum, though by far the most interesting hemorrhages are those of the retina. These were so thoroughly investigated by Horner that, according to H. Müller, further observations have added nothing new. "The ophthalmoscopic picture is characterized by an extreme pallor of the optic

papilla and the whole posterior eyeground, by marked tortuousness and dilatation of the veins, by pallor of the blood in the vessels, and by apoplexies. These last usually lie near the vessels, are of round irregular or linear shape, and are distributed in small or larger numbers throughout the entire circumpapillary region. They are sometimes quite small, punctate, again somewhat larger, and in individual cases reach even the size of the papilla. The number of hemorrhages, while at first small, frequently increases toward the end of life, the rest of the posterior eyeground, especially the papilla, becoming continually paler, eventually even white. The amount of extravasated blood is ordinarily slight; the areas of extravasation are thin and frequently show transparent margins. On the pale rose-red posterior eyeground we occasionally see areas from which the blood has been absorbed, though this is relatively rare. When the eye is examined early, no apoplexy is found, though the posterior eyeground is even then striking on account of its intense pallor and the marked tortuosity of the vessels. Reversely in cases which recover we can see on repeated ophthalmoscopic examination how all the hemorrhages are gradually resorbed, how the vessels return to their normal size and straightness, and the deep pallor of the papilla gradually gives way to its normal rosy tint."

Nothing of importance can be added from the later literature to this description of Horner's. The opinion of ophthalmologists is divided only in regard to the white center of the extravasate, which Horner regards as a focus of absorption (compare the section on Pathology).

An absolutely isolated observation, unfortunately not confirmed by a post mortem, comes from H. Müller, in regard to the development of exophthalmos during the disease.

While retinal hemorrhages occur almost unexceptionally in all cases of progressive pernicious anemia (Laache described a negative case (Case 3) eight days ante mortem), coarse derangements of vision according to all authorities are extremely rare. From his large amount of material H. Müller gives one interesting example: A patient (a female) became suddenly blind in the left eye; ophthalmoscopically enormous hemorrhages in the form of thick plaques were found in the retina, especially in the region of the macula.

[De Schweinitz[1] in a study of the histology of the eye in pernicious anemia states the following conclusions: "In summary I may say that the histologic changes found in this case were: (*a*) hemorrhages in the various strata of the retina, but most marked in the nerve-fiber layer; (*b*) varicose hypertrophy of the fibers of the nerve-fiber layer, existing

[1] *Trans. Amer. Ophthal. Society*, 1896.

either as an isolated lesion or sometimes gathered in a conglomerate mass; and (c) exquisite edema of the retina, especially in its periphery, an edema beginning in the outer reticular layer and gradually involving the outer granular layer, until the space between the internal nuclear layer and the outer limiting membrane becomes riddled with a series of oval cavities.

"These microscopic findings correspond closely with the ophthalmoscopic picture: (a) flame-shaped and irregular hemorrhages in the neighborhood of the papilla; (b) hemorrhagic areas containing a yellowish center, or isolated yellowish-white spots which probably correspond to the hypertrophied and degenerated nerve-fibers which have been described; and (c) a cloud-like edema, which was most marked in the retinal periphery."

Uhthoff[1] had described certain colloid bodies in the intranuclear layer, and Manz[2] found round cells enclosed in a capsule, which he believed to be a dilated capillary. De Schweinitz could not find either of these formations. Natanson[3] examined the eyes in 3 cases of parasitic pernicious anemia and found the same microscopic and ophthalmoscopic conditions as have been discovered in other forms of pernicious anemia.—ED.]

Eichhorst reports several observations on disturbances of hearing. Apart from the ringing in the ears common to all anemias, we may find, especially toward the end of life, a complete loss of this sense.

Among 5 cases that ended fatally, Eichhorst found only 1 in which hearing remained intact. In several of his patients the deafness was transitory, and in 1 it was restored after a transfusion of blood.

The writers must likewise draw on Eichhorst in regard to the disturbances of smell. Eichhorst observed a considerable loss of smell in association with deafness shortly before the end. A further modification was added in a marked decrease of the sense of taste. In this case one certainly has to do with an exception; at least Schauman reports that in his large amount of material he never saw a single anomaly of smell or taste.

PATHOLOGIC ANATOMY.

In cadavers of persons that have succumbed in the natural course of an uncomplicated progressive pernicious anemia the pallor of the skin is so characteristic in intensity and color that, as in a living subject, a proper diagnosis may be made at a glance.

[1] *Klin. Monatsbl. f. Augenheilkunde*, 1880. [2] *Centralbl. f. die Med. Wiss.*, 1875.
[3] Nagel's *Jahresbericht der Ophthal.*, xxv., 1895.

We can occasionally, and according to Ponfick frequently, make a diagnosis from the presence of icterus, edema, and the almost unexceptionally good preservation of the subcutaneous fat.

A sign and a result of the emptiness of the vessels is the frequent complete absence of postmortem lividity (H. Müller).

Among the general postmortem symptoms we have the **intense anemia** of all the internal organs and the widespread **hemorrhages.** These are very evident in the skin and mucous membranes provided they occur shortly before death. Hemorrhages are likewise found to a greater or less extent on the serous membranes of the three body cavities, though most frequently on the meninges.

The abnormal **amount of iron,** "siderosis," in the internal organs observed by Grohe and later by Rosenstein, Quincke [Peter, Scott], and many others, and missed in but few cases, stands in a certain though not very clear connection with the hemorrhages. Still, according to frequent postmortem reports, the same organs that show an unusual excess of iron in one case may in another parallel case contain only the smallest normal amount. The objection raised especially at the beginning of the studies on this subject, that the increased iron content of the organs was not the result of the diseased process, but of the therapeutic administration of the metal, is controverted by animal experiments (Quincke), and especially by the fact that this abnormality is no less frequent since iron has been practically done away with in the treatment of pernicious anemia.

We find an abnormal increase of iron primarily in the organs which make and destroy the blood-elements, and which show physiologically a considerable amount of iron, namely, the spleen, the bone-marrow, the lymph-glands, and most especially the liver. Moreover, iron is observed in situations where it is normally lacking, as the glandular cells of the kidney and the pancreas.

The difference between the amount of iron found physiologically and in progressive pernicious anemia is, according to Quincke's statistics (compare "iron therapy"), most evident in the liver. Under normal conditions 100 gm. of dried liver substance contains 81.6 mg., while cases of progressive pernicious anemia showed an increase to 1900 mg. (Stühlen). Microscopic examination demonstrated that the increased accumulation of iron was manifest in fine granules deposited in both the liver-cells and the capillaries in the peripheral parts of the liver-lobules. [Hunter states that the average amount of iron found in the liver in pernicious anemia by various observers was 0.7 per cent., while the amount found in other diseases was from 0.078 to 0.12 per cent.

In a recent paper Hunter[1] has compared the findings in 7 autopsies in pernicious anemia with those of 7 cases of secondary anemia due to sepsis, carcinoma, and other diseases. The average percentage of iron in the liver and kidneys was 0.360 in pernicious anemia as compared with 0.079 in other conditions; and in the spleen 0.125 in pernicious anemia as compared with 0.362 in other conditions. J. A. Scott examined for Osler (*Principles and Practice of Medicine*) the livers in 45 cases of diseases other than pernicious anemia, and consistently failed to find the iron deposits characteristic of the latter disease.—Ed.]

The **musculature** of the trunk and the extremities shows, according to Eichhorst, like all other organs, a marked pallor, while H. Müller expressly notes its "good color" in contrast to the pallor of other organs. A reverse contradiction exists between the microscopic observations of these two authorities, Eichhorst finding the macroscopically very pale musculature almost entirely normal in structure, while Müller found in the muscles of good color a pronounced fatty degeneration of the fibrillæ. This degeneration was most marked in the muscle-fibers of the diaphragm and of the intercostal muscles, in which the cross-striations were almost entirely obliterated.

Though Eichhorst, following a conception of Traube's, claims that when fatty degeneration occurs it is most marked in those muscles which display a vitally necessary unceasing activity—*i. e.*, in the diaphragm and the intercostal muscles—E. Fränkel describes a case in which the general musculature was normal, while the ocular muscles and the heart manifested advanced fatty degeneration. In appearance they were clay colored, their cross-striations were almost absent, and fat and pigment were readily perceived in and between the primitive bundles. Though the functions of the ocular muscles are not a requirement for the continuance of the vital processes, it can not be doubted that even in conditions of extreme weakness, when the patient avoids every movement of the voluntary muscles, relatively a great demand is made upon them.

The deposition of pigment, which has been mentioned, between the bundles of muscle-fibers usually represents the remains of old hemorrhages. Recent hemorrhages are likewise sometimes encountered (Stricker and others).

A very prominent place is occupied by the anatomic changes in the **heart.** Brief mention may be made of the fact that the fat infiltration is retained, and that in the pericardium, in the muscle, and in the endocardium extravasations of blood are found as in other organs. Since the beginning of the investigations on progressive pernicious anemia,

[1] *Lancet*, Jan. 31 *et seq.*, 1903.

the greatest interest has been aroused by the *fatty degeneration of the myocardium.* We owe to Ponfick the fundamental anatomic investigations, but these have been completed by later scarcely less important ones.

On section, the musculature of the heart shows all grades of pallor between a pale brownish-red and a clay color. Since all these grades of color are found in the same heart, and the clearer areas in the form of flakes or lines appear to have pushed their way into the less decolorized large mass of muscle, the organ exhibits a very characteristic appearance. The clearer the areas the more intense is the fatty degeneration microscopically. Moreover, when very marked, though the fibrillary arrangement may be recognizable, the cross-striations and muscle-nuclei disappear; in place of the latter we find very fine fat-drops arranged like pearls on a necklace. In the macroscopically darker areas the muscular structure is better preserved, and the cross-striation is still apparent even though slight clouding may be noticeable. Isolated portions may be completely normal.

The distribution in the different stages of degeneration manifests a remarkable regularity. The fatty degeneration is more marked in the papillary muscles of the left heart than of the right, than in the walls of the left and right ventricle, and the trabeculæ of the left and right auricle.

This degeneration of the heart is found in almost every case of progressive pernicious anemia, so that since Biermer's time it has been considered one of the cardinal symptoms in the general picture. Still, isolated observations must be mentioned in which it was absent, although from the clinical course and the general anatomic findings there could be no hesitancy in retaining the diagnosis of progressive pernicious anemia. Such cases have been reported by Litten, H. Müller, and later by Stricker, Quincke, and Laache.

Fatty degeneration of the heart, therefore, can not be regarded as absolutely constant. Moreover, it must be remembered that similar alterations occur in other anemic conditions, for instance, the acute post hemorrhagic.

The heart is usually of normal size or a little smaller than normal, sometimes the right ventricle is found somewhat dilated; slight hypertrophy of both ventricular walls has been mentioned by Eichhorst.

Corresponding to the fatty degeneration the consistence of the muscle is less than normal.

The *valves* are normal. Even in cases in which a diastolic murmur was heard the valves were found intact (Biermer), a proof of the fact

that a diastolic murmur may also be accidental. The mitral insufficiency reported in one case by Schauman must be considered a coincidence. Mention may also be made of an anomaly of the mitral valve found in 1 case by Matterstock, in which the tips of the leaflet were found bound together. In this case the diastolic murmur heard during life was undoubtedly due to this anatomic abnormality.

According to the unanimous reports of all postmortem protocols, the *larger vessels* manifest no typic alterations. The small arteries and capillaries, on the contrary, especially those of the brain, frequently show fatty degeneration, and to this must be attributed the occasional extensive apoplexies. Smaller hemorrhages may occur without perceptible fatty degeneration of the vessels. For these cases we assume with Cohnheim that the deteriorated blood produces alterations of the vessel-walls which we are unable to perceive by the aid of our present methods.

The **kidneys** are extremely pale, but otherwise present no macroscopic abnormality; the capsule is easily stripped, the superficial surface is smooth. In the cases described by Fr. Müller in which he is inclined to assume a connection between progressive pernicious anemia and syphilis, deep cicatrices characteristic for the syphilis were found on the surface. Microscopically we sometimes see (Ponfick, Eichhorst) fatty degeneration of the desquamated epithelium and a marked deposition of iron in granules. In a case reported by Krebs the desquamated epithelium of the kidney as well as that of the liver and intestinal villi showed amyloid degeneration.

In the remaining portion of the urogenital apparatus we find, apart from hemorrhages, no alterations worthy of note.

In regard to the **respiratory apparatus**, which also plays a very insignificant clinical rôle, mention must be made of rare hemorrhages into the parenchyma of the lungs (Schumann) and more frequnt ones on the pleura. An observation of Eichhorst's is in place, since the finding of the condition might readily give rise to diagnostic difficulties, namely, he found the fluid of a hydrothorax three times evidently sanguinolent, and once evidently icteric.

The pathologists have lately paid especial attention to the **digestive tract**, and to this we owe a considerable proportion of our knowledge in regard to the etiology and pathogenesis of the disease.

In the first place, we find, besides a marked pallor, ecchymoses throughout the whole tract. Quincke described in 1 case a marked edema of the gastric mucous membrane.

Ponfick was the first (1873) to call attention to the alterations, par-

ticularly the fatty degeneration of the *gastric glands* in severe anemias. In his dissertation, published in 1875, Schumann described a case of progressive pernicious anemia in which the gastric mucous membrane was almost completely denuded of its epithelium and the gastric glands were poorly developed and insignificant in number. In addition, numerous small hemorrhages, an overgrowth of connective tissue, and some fatty degeneration of the muscularis and of the blood-vessels were found. This case is an illustration of the alterations to which later investigators have devoted so much attention. Moreover, Quincke's observation must not be omitted, which though it was published first in 1876, came from a postmortem protocol (Case 6) of February, 1875. In this he describes a very thin, pale gastric mucous membrane extremely poor in glands. Quincke then attributed the origin of the progressive pernicious anemia in this case to these atrophic alterations. [Henry and Osler described an analogous case.—Ed.] A large number of isolated observations followed Quincke's report, and supplemented it by finding similar alterations in the intestine. Recently, Ewald, Martius, and Koch have studied and described these conditions.

In the severest cases the mucous membrane is smooth, shows almost no valvulæ conniventes, and is considerably reduced in thickness. In 1 case of Martius' it was on an average scarcely 1 mm. This marked thinning may be recognized macroscopically in the submucosa and the muscularis. This condition may be found in all sections of the intestine from the duodenum to the colon.

The microscopic examination shows a marked overgrowth of the interglandular tissue in the mucous membrane of the stomach and intestine, which in the earlier stages is characterized by its richness in round cells, while in the later stages it is very poor in cells and is fibrous. The more advanced the growth of this tissue, the more the glandular portion is compressed; although in moderately severe cases numerous isolated glands or their remains may be found, especially in the deeper layers of the mucosa, in the very severe the process leads to a complete disappearance of the glandular portion. Small depressions in the connective tissue containing a finely granular detritus and corresponding to the previous excretory duct are left to indicate the former structure (Martius).

[H. Strauss[1] opposes the view that there is a relation between pernicious anemia and disease of the gastro-intestinal tract. His studies in 10 cases showed a richness of the mucous membrane of the gastro-intestinal tract in lymphocytes, but practically no evidence of disease

[1] *Berlin. klin. Wochenschr.*, August 25 and Sept. 1, 1902.

of the stomach or increase in the connective tissue. The lymphocytic accumulation is not a special change in the stomach, but a part of a general involvement of the lymphoid tissues analogous to the changes found in the bone-marrow.—ED.]

Since the writers must refrain from going too deeply into detail, they will mention only two other interesting findings which were observed in the atrophic mucous membrane of the stomach, but not in the intestine. Lubarsch found in the interstitial tissue of all his cases numerous eosinophile cells, an observation which recalls Hammerschlag's in gastric cancer. Further, Lubarsch and Koch found in the interglandular tissue roundish sometimes roughly irregular bodies varying in size from an eosinophile granule to double that of an epithelial cell. With high powers it could be seen that the larger bodies were not homogenous, but were made up of a number of smaller elements. On staining with Biondi's fluid they took the acid fuchsin. Koch regards them as coagulated red blood-corpuscles, Lubarsch as acidophile granules which have run together in smaller and larger clumps. Both authorities agree that they are pathognomonic of the atrophy of the mucous membrane on account of their regular occurrence. The "hyaline bodies" described by Sasaki are apparently identical with them.

Moreover, not only the mucosa, but also the other layers and components of the stomach and intestinal walls may be affected by degenerative processes. Jürgens first called attention to a progressive degeneration of the motor nerve-elements of the intestine and of the general musculature. Sasaki confirmed this finding, and Blascko described a case with extreme degeneration of both Auerbach's and Meissner's plexus. A considerable diminution in thickness of the intestinal muscularis is recognizable in such cases, even macroscopically. These findings made a basis for the theory that in certain cases of progressive pernicious anemia the primary cause is the destruction of the nervous elements of the intestine which necessarily leads to marked functional disturbances, and these in turn to severe anemia. The observation made by Sasaki, however, opposes the primary nature of the nerve degeneration; that is, in a case in which the lesions in the intestine were more insular, the changes in the nerves did not correspond with them.

This degeneration of the gastro-intestinal wall, for which Jürgens proposed the name "atrophia gastro-intestinalis progressiva," and for the terminal stages of which Ewald's designation "anadenia" is appropriate, is in no way specific of progressive pernicious anemia, since it is wanting in numerous cases. How large a percentage of all cases show these

gastro-intestinal alterations is yet unknown, though they are apparently found in a preponderating majority.

On the other hand, marked atrophy of the stomach and intestine has been not infrequently described in conditions which were absolutely differentiated from progressive pernicious anemia. For instance, Fenwick described it in numerous cases of mammary carcinoma, Kussmaul and Maier in 1 case of chronic saturnism, and competent authorities in a series of other diseases.

Though the theory of the specificity of the gastro-intestinal process in progressive pernicious anemia seems decidedly endangered by these statistics, there is still reason for the assumption that the profound alterations of the intestinal tract and the consequent inevitable disturbances of nutrition, may constitute the cause in at least a certain group of cases. Almost all the investigators who observed atrophy of the intestine regarded it as the cause of the anemia; for instance, Fenwick, Kussmaul and Maier, and others believed that it had produced pronounced secondary anemia; Quincke, Martius, and others considered it the cause of the essential anemia.

[Bloch,[1] in discussing the etiology of pernicious anemia, refers to some experiments made for the purpose of determining whether intestinal fermentation exercises any particular influence. Extracts made from the intestinal contents of patients in different stages of the disease were injected into animals without producing characteristic symptoms, and the results were practically the same as those obtained from similar extracts got from healthy persons.

Estimations of the ethereal sulphates gave varying results, and the author found indicanuria, on which Grawitz lays some stress, an inconstant condition. When present, he found it due to constipation.

Determinations of the toxicity of the urine also gave uncertain results. If there were a diminution in the normal excretion of toxins or an abnormal formation of toxic bodies, an increased toxicity of the blood would result. Neither condition could be proved. The blood-serum from patients showed no special toxicity for mice or guinea-pigs.

Einhorn[2] comes to much the same conclusion as Bloch, and in discussing the relationship of achylia gastrica to pernicious anemia, he concludes that no special relationship exists. In most cases of achylia gastrica the blood is practically normal, even though the change in the stomach is extreme. On the other hand, in pernicious anemia the gastric juice is secreted in normal quantity and is of normal character.

[1] *Deutsch. Arch. f. klin. Med.*, vol. lxxvii., Nos. 3 and 4.
[2] *Med. Record*, February 23, 1903.

The two conditions may occur together, but the association, he thinks, is not a close one.

H. Adler[1] describes 3 cases of pernicious anemia associated with achylia gastrica. He considered the anemic condition secondary to the gastric disease.

Strauss,[2] in an investigation of the relation of gastro-intestinal conditions and anemia, especially pernicious anemia, notes that experimental obstruction of the intestine in rabbits produced no marked or characteristic change in the blood and studies of the hemolytic power of the blood serum of persons suffering with constipation showed no differences from the serum of normal individuals. He insisted that no relation between gastro-intestinal disease and pernicious anemia has been established.—ED.]

In another section were shown the difficulties encountered in the endeavor to explain anemic conditions from disturbances of nutrition. Since it was proved that quantitative undernourishment can not lead to anemia, and qualitative undernourishment only under very definite circumstances, toxic substances elaborated within the intestinal tract in the course of disturbances of digestion and absorption have been made responsible for its origin. The genesis, therefore, may be stated as follows: The primary process is the atrophy of the gastro-intestinal mucous membrane; this produces severe disturbances of absorption, etc., and these in turn the severe anemia. (Martius attributes decided significance only to the atrophy of the intestine, not to that of the stomach.)

This hypothesis, however, does not agree with the detailed investigations of Koch in the Berlin Pathologic Institute. In 5 cases of progressive pernicious anemia examined by him death was produced by the disease itself without any complication. If the relations between the anemia and the atrophy of the intestine were as above represented, a gastro-intestinal atrophy of the highest grade should have been found in all cases, yet Koch expressly insists that in 3 of his cases the mucous membrane of the intestine showed only a slight degree of atrophy. The theory of the primary nature of the intestinal disease and the secondary nature of the severe anemia is thereby demolished. Moreover, an interesting clinical observation creates a crucial objection. Schauman examined 16 persons who had been cured a long time previously, some of them even years before, of a bothriocephalus anemia and had recovered perfect health. In 10 he found that the gastric juice contained no free hydrochloric acid. If the

[1] *American Medicine*, November 15, 1902.

[2] *Berlin. klin. Woch.*, August 25–September 1, 1902.

stomach disease was the cause of the severe anemia, the symptoms of the former should have disappeared before the latter.

We come, therefore, to the other question, Is the progressive pernicious anemia the foundation on which the gastro-intestinal atrophy develops, or are both the result of one and the same still unknown cause? It is possible that in this regard the progressive pernicious anemia with known cause will prove explanatory. Schauman, in his monograph on bothriocephalus anemia, unfortunately reports only the macroscopic examination of the intestine, though this not infrequently showed the intestinal wall considerably thinner than normal; Eckert, however, reports that the gastric and intestinal mucous membrane were atrophic in 1 case of tapeworm anemia. Nevertheless taken altogether profound gastro-intestinal alterations have been found in only a small portion of the cases of bothriocephalus anemia which came to autopsy, while the majority showed no coarse changes in the intestinal canal in spite of the severe anemia. If we contrast these observations with those in which we found similar intestinal lesions in other diseases without severe anemia, we can only assume a coördinate origin of both symptoms, the anemia and the atrophy.

This conclusion recalls the one on the relation of the alterations in the spinal cord to progressive pernicious anemia (see p. 275); we must, therefore, assume the same cause for the anemia, the intestinal atrophy, and the spinal degeneration. What circumstances are necessary in order that one and the same influence may produce sometimes one, sometimes the other lesions, sometimes all of them together, is at present a mystery.

In concluding this discussion the writer would like to state that the anatomic alterations of the intestine do not always correspond to the digestive disturbances observed during life. Thus Quincke reports that no anatomic alterations of the digestive tract could be found that correspond to the intense clinical symptoms, and, reversely, cases have been reported by Eisenlohr and Martius which manifested during life almost no disturbances of digestion and a pretty good condition of nutrition, while the section showed a very severe atrophy of the intestinal wall.

Nothnagel reported in 1 case of progressive pernicious anemia a marked thinning of the mucous membrane associated with disappearance of the gastric glands and an enormous thickening of the gastric wall due to an overgrowth of connective tissue. The rigid walls which grated under the knife surrounded a cavity corresponding to about the size of a large pear. [The editor has observed a case exactly like that of Nothnagel.—Ed.]

In the section on the pathogenesis of the progressive pernicious

anemia, moreover, the writers have mentioned several cases of the disease in which autopsy revealed carcinomata in early stages. For the significance of this finding, see p. 243.

In a pretty large number of cases presenting otherwise nothing characteristic, not even a splenic tumor, the *mesenteric glands* were found enlarged (Eichhorst, Quincke, and others). According to the microscopic investigations of Eichhorst the enlargement proved to be a pure hyperplasia and in only 1 case was a caseous degenerated center observed. What relation these enlarged lymph-glands bear to the disease-process, and whether they are associated merely with local disturbances in the intestinal tract or with the abnormal function of the bone-marrow, can not be determined. In the blood we find no evidence of an increased activity of the lymph-glands as far as the production of lymph-cells is concerned.

[A. S. Warthin[1] has contributed some very interesting studies of the pathology of pernicious anemia based upon an investigation of 8 cases. His studies were mainly directed toward the hemolymph nodes, which he believes play an important part in the pathology. He considers the disease especially an hemolytic one, and thinks that some unknown poison stimulates the phagocytes of the spleen, lymphatic glands, hemolymph-glands, and bone-marrow. The hemolysis is not confined to the portal area, as Hunter maintained, but is apparent in the prevertebral lymph- and hemolymph-nodes and in the bone-marrow. In most cases, however, the spleen is the chief seat of blood destruction. He could find no pathologic evidence of hemolysis in the liver, stomach, or intestinal capillaries in any of his 8 cases.

The changes found in the hemolymph-glands were dilatation of the blood-sinuses and evidences of increased hemolysis. In some cases great increase in the size and number of the hemolymph-glands was conspicuous. These changes, however, are not specific of pernicious anemia. The lymphoid and megaloblastic changes in the bone-marrow the author considers merely compensatory in nature, and not an essential part of the pathology. Enlargements of the lymphatic glands similar to those noted by Warthin, but not confirmed by accurate histological studies, had been observed by Eichhorst, Weigert, Kohler, and Müller (quoted by Warthin). Most authors are silent as to the condition of the lymphatic glands.—ED.]

The anatomic changes in the **liver** are very variable. In one group of cases this organ is striking on account of its almost normal reddish-brown color. The enlargement occasionally found was studied

[1] *Amer. Jour. Med. Sci.*, Oct., 1902.

microscopically by Gilbert and Garnier in 3 cases, who described it as a true hypertrophy. Again the liver is frequently pale, even somewhat clay colored and smaller than normal. Ponfick demonstrated the participation of the liver in the general fatty degenerative process. This is recognizable macroscopically; under the microscope it is found to affect the hepatic and vascular cells. In 1 case Krebs described amyloid degeneration of the liver-cells. In regard to the appearance of iron in the liver, see the general discussion of Siderosis on p. 141.

In confirmation of clinical observations the **spleen** is usually found either normal in size or smaller than normal. In rare cases a slight firm enlargement has been observed. Considerable enlargement, even to double the normal, has been reported by Wilks and Rosenstein, the latter's case arising after typhoid fever. It follows, therefore, that large splenic tumors must be regarded as accidental coincidences or as sufficient grounds for a reconsideration of the diagnosis. [Warthin[1] found the spleen enlarged in 4 out of 7 cases examined post mortem. In 1 of these cases the organ was twice the normal size; in another four times the normal size. Other references to enlargement of the spleen have been added in the clinical section.—Ed.] Mention has been previously made that this organ takes considerable part in the siderosis. In general the microscopic examination of an enlarged spleen shows a simple hyperplasia.

The alterations in the central and peripheral **nervous system** are, on acount of the clinical symptoms, of very great interest. The macroscopic observations of the early investigators left little to be added later. Nevertheless a series of valuable microscopic discoveries was reserved.

The first striking feature is the conspicuous part taken by the **brain and its membranes** in the general hemorrhagic diathesis. The dura mater shows, as was reported by Biermer, H. Müller, Eichhorst, and others, especially on its internal surface, numerous larger or smaller extravasations of blood. These extravasations become organized and form very fine transparent membranes, which, according to H. Müller, consist of a delicate network of fibers filled with the remains of the hemorrhages. Their extent is very variable, and occasionally they stretch over the whole cerebral convexity. The external surface of the pia shows similar extravasations and pseudomembrane formations.

In the large majority of cases described in the literature, the anatomic investigation of the brain showed no abnormality beyond the anemia. Biermer, H. Müller, and Schüle found small extravasations of

[1] *Trans. Assoc. Amer. Physicians*, 1902.

blood in different cases that presented no outspoken cerebral symptoms during life. Birulja first reported a microscopic examination of the brain in a case of progressive pernicious anemia. He found numerous blood extravasations, irregularly distributed, together with numerous round cells in the vicinity of the hemorrhages in the cerebral cortex and in the pericellular spaces of the nerve-cells. Moreover, in the cerebral cortex, in the medulla, and in the cerebellum these cells showed alterations consisting in the deposition of pigment, vacuolization, swelling, and diminution of staining power to carmine.

These represent the scanty observations found in the literature on the anatomic alterations of the brain; still it must be added that an examination of the brain was undertaken in but few cases, and that the finer methods of Marchi and Nissl were not employed. It is to be hoped that the gaps will soon be filled.

The anatomic alterations in the **spinal cord** are very variable. In general, degeneration affects preferably the upper sections of the cord, especially the cervical and thoracic portions; the lumbar portion is affected more rarely. Still lesions are sometimes found throughout its whole length.

We find in the first place, as in the brain, *hemorrhages* corresponding to the general tendencies of the disease. Eisenlohr found numerous capillary hemorrhages in the gray substance of the thoracic cord with subsequent overgrowth of the glia. Still, among the cases described, spinal cord hemorrhages are rare. Moreover, they are completely independent of other degenerations, and can by no means be regarded, as Teichmüller claims, as their starting-point.

The anatomic alterations in the **gray substance** play a comparatively small rôle. Even with extensive lesions in the white substance they may be entirely absent or very slight. Rothmann observed an almost complete disappearance of the medullated fibers in the anterior horns, while Clark's columns and the ganglion-cells of the anterior horns remained intact. Boedeker and Juliusburger and Brasch found alterations in Nissl's bodies, slight swelling of the nucleolus, and marked pigmentation.

Most important, because most frequent and most extensive, are the alterations of the **white substance.** The starting-point for all the degenerations is furnished by very small foci which are situated, as a rule, in the vicinity of vessels, and which show a very circumscribed degeneration of the nerve-fibers and often a secondary growth of nervous connective tissue. These small foci usually run together into larger plaques. Further disturbances then arise on account of secondary de-

generation of the nerve-tracts included within these foci. Since the long tracts of the spinal cord lie next one another, conditions are found after the degeneration has advanced which simulate combined columnar scleroses. The genesis of these alterations, however, shows that they in no case hold strictly to the columns. The apparent columnar degenerations are found especially in the posterior columns, which do not remain entirely intact in any case of spinal disease. The formation of foci in other columns is very variable and the participation of the lateral and anterior columns is extremely irregular.

[In his study of 7 cases Burr found the cord normal in but 1. The lesions were fairly constant. The cervical swelling was always the principal seat of change, from which point downward there was a gradual decrease in the pathologic condition until in the lumbar enlargement a normal condition was usually found. He notes, however, that in Bowmann's case the lumbar cord was involved. The parts of the cord affected are the posterior columns, the lateral columns in and near the crossed pyramidal tracts, the direct pyramidal tracts, and rarely a band running forward along the circumference of the cord (direct cerebellar tract). The gray matter is rarely affected even slightly.—Ed.]

Finally, mention must be made of the alterations observed in the *vessels* of the white and gray substance (Minnich, Nonne, et al.) which are possibly of importance in the genesis of the focal affection. These investigators found sometimes the lumina of the vessels dilated, again the walls thickened, from hyaline degeneration. Jacob and Moxter found the thickening of the walls so marked that the lumina of the vessels had disappeared.

The *peripheral nerves* are described by the majority of observers as completely intact. V. Noorden reports, however, the microscopic investigation of the two crural, tibial, and peroneal nerves in 1 case in which extensive alterations were found in the spinal cord. The peroneal nerves were normal. The other two pairs showed about two- to three-fifths of the individual nerve bundles degenerated. The medullary sheaths were swollen and broken into irregular masses. The axis cylinder lay intact in the midst of the broken-up medulla. The nuclei of the medullary sheaths were scarcely increased, the vessels and connective tissue showed no evident alterations. (Positive clinical symptoms of a peripheral disease were not observed in this case.)

In regard to the changes found in the eye post mortem, nothing of importance is to be added to what has been said in the clinical part. The autopsy completely confirms the ophthalmoscopic finding. The microscopic investigation of the retinal lesions has led to a divergence

of views. Horner considers the whitish discoloration which gradually arises in the center of the small extravasation as a sign of absorption; Manz claims that it is produced by a collection of round cells; Uhthoff regards it as the expression of a true retinitis. [De Schweinitz coincides in this opinion, and has reported an interesting study, already referred to in the clinical section.—Ed.] Eichhorst showed that the effusion of blood into the retina arose, at least sometimes, from an aneurysmal dilatation of the vessel wall with subsequent rupture, though undoubtedly some of the hemorrhages are explicable only by diapedesis. E. Fraenkel found in 1 case a marked fatty degeneration of all the ocular muscles with a rich accumulation of pigment in and between the primitive bundles.

Hemorrhages are also found among the pathologico-anatomic findings of the *organ of hearing*. Habermann describes them in 1 case in the right ear, between the nerve-fibers and ganglion cells in the cochlea, the vestibule, and the semicircular canals. The vessels in the vicinity of the hemorrhages showed no aneurysmal dilatations as they do in the retina, and, therefore, we must attribute the hemorrhages to diapedesis.

Several cases have been described in the literature in which lesions were observed in the **skeleton.** The best known is a frequently quoted case of Fede's. This was a severe anemia, the cause of which was found in multiple tumors of the heads of the third to the ninth ribs, associated with alterations in the bone-marrow. Since the blood examination was defective, it is impossible to judge whether this case should be reckoned with progressive pernicious anemia or not.

E. Grawitz mentions in a late publication a case of severe anemia following syphilis, which he was inclined to consider an early stage of progressive pernicious anemia, and in which he found by the Röntgen rays a thickening of both tibiæ and femora. The blood finding in this case seems scarcely such as would justify a diagnosis of progressive pernicious anemia.

In the pathologic anatomy of progressive pernicious anemia the **bone-marrow** demands careful consideration on account of its importance as a blood-making organ.

The first investigator, omitting the incomplete statements of several of his predecessors, who accurately described the changes in the bone-marrow in progressive pernicious anemia and recognized them as a very important symptom of the disease, was Cohnheim. In his celebrated work of the year 1876 he mentions a case in which the autopsy showed the fatty marrow of the long bones replaced by a raspberry

jelly-like mass. Closer investigation revealed that this corresponded to the normal marrow of spongy bones. On microscopic examination, Cohnheim found that this marrow was almost devoid of fat-cells and consisted of about equal parts of colorless cells of different sizes and hemoglobin containing cells. Some of the latter had exactly the appearance of normal red blood-corpuscles, others showed a much larger diameter, and a great number were nucleated, especially among the larger varieties.

This discovery of Cohnheim's acted as a stimulus for innumerable investigations along the same line (for the literature, see Geelmuyden), which confirmed Cohnheim's finding, even though differences of opinion arose as to its significance. The principal discussion arose over the question whether the alterations in the bone-marrow should, with Cohnheim, be regarded as the primary process which produced the anemia, or whether, as E. Neumann explained them, they should be considered an endeavor on the part of the organism to compensate for the anemia.

The value of Cohnheim's observation was, to a certain extent, modified by the fact that a transformation of yellow fatty marrow into red lymphoid marrow had been described by E. Neumann in 1869 "in chronic diseases which led to marasmus"; and further by the fact that cases of progressive pernicious anemia were reported by competent authorities (Laache, Quincke) in which this transformation did not occur. The theory, therefore, of the essential importance of these alterations for progressive pernicious anemia seemed demolished.

Geelmuyden showed that the transformation of fatty marrow into lymphoid marrow was not a characteristic feature of progressive pernicious anemia, but that the transformed bone-marrow in this disease may be readily differentiated microscopically from the new formed lymphoid marrow of other anemic, cachectic, and febrile conditions. The lymphoid marrow of the long bones in the latter series of conditions exactly resembles in its microscopic features the physiologic lymphoid marrow of the vertebræ, the sternum, and the ribs, and consists of exactly the same elements. In addition to several elements unnecessary to take into consideration here, it regularly contains nucleated red blood-corpuscles corresponding in size with normal red blood-corpuscles and distinguishable from the small colorless cells of the marrow only by their hemoglobin. In these cases, therefore, the transformation represents only a simple increase of the physiologic function of the bone-marrow, a process which is most readily explained as one of reaction and regeneration.

The lymphoid marrow of the long bones in progressive pernicious

anemia, however, is distinguishable from this, in that, although it resembles the physiologic red marrow in its general elements, the nucleated red blood-corpuscles show decided differences. They are in the first place of large size and may exceed by three times the diameter of the normal; in the second place they manifest by their striking dark color a higher hemoglobin content, and thirdly, they show an inclination to take an oval rather than a round form. The lymphoid marrow of progressive pernicious anemia, therefore, is characterized by its number of megaloblasts, cells which are foreign to the adult organism. Consequently, even if this metamorphosis of the bone-marrow is considered a regenerative process, it stands far behind that of simple anemia in value.

In addition we see elements which, though not exclusively characteristic of progressive pernicious anemia, are more numerous than under any normal condition, namely, large giant cells containing several (eight, ten, or sometimes more) red blood-corpuscles. Moreover, we find an increased deposition of pigment in and between the marrow-cells. Both of these conditions indicate an increased destruction of red corpuscles.

[Ewing[1] states that he has found three rather distinct conditions in the marrow of the ribs, the vertebræ and femurs of fatal cases of idiopathic pernicious anemia.

1. The Cohnheim-Rindfleisch type (megaloblastic degeneration), in which with wide extension of lymphoid marrow an excessive proportion of the cells in the marrow and nearly all the nucleated red cells are megaloblasts or gigantoblasts.

2. Extreme lymphoid hyperplasia (myeloblastic degeneration), in which the majority of cells are small, hyaline, and mononuclear, while nucleated red cells are scarce, and those remaining are of large size. This type of lesion is identical with that recently described by Naegeli under the term "myeloblastic degeneration."

3. Recently the writer encountered a case of fatal pernicious anemia of twelve months' duration, without demonstrable origin, in which the marrow showed a remarkable excess of nucleated red cells of normal size.—ED.]

These statements in regard to the macroscopic and microscopic alterations of the bone-marrow require amplification.

In the first place the extent of the alterations varies within wide limits in individual cases. At one end of the series we have rare cases like that described by Rindfleisch. In this the entire marrow of the

[1] *Clinical Pathology of the Blood*, 1903.

tubular bones was transformed into lymphoid tissue, and on microscopic examination was found to consist exclusively of megaloblasts. Next to such cases stand others in which the entire fatty marrow is transformed into red marrow, but besides megaloblasts and gigantoblasts, numerous cells of normoblastic type are found. In still another series we find the bone-marrow only partially replaced by red marrow, and the relative number of megaloblastic cells diminishing till, in some cases, they appear only in isolated areas. The series closes with those cases in which, in spite of severe universal anemia, not the slightest metamorphosis of the fatty marrow is found (Ehrlich, Geelmuyden, C. S. Engel). [Lipowski,[1] Muir,[2] and Ewing[3] have reported similar cases.—ED.]

If we weigh the significance of these differences, we must agree with E. Neumann, whose arguments have been generally convincing, that the lymphoid transformation of the fatty marrow is not the primary process which produces the anemia, but is an attempt on the part of the organism to make good the losses arising from the anemia.

Just as the varying clinical manifestations of different cases of anemia have sometimes been regarded as merely gradations in intensity, so the alterations in the bone-marrow have been regarded as graded reactions to the same variety of irritation (Muir), and have been represented as follows: 1. All influences tending to produce anemia stimulate the normal bone-marrow so that the increased blood destruction will be met by an increased blood formation. This occurs when the normally inactive bone-marrow takes up the hematopoietic function. 2. If the anemic influence continues its action for a longer time, or is more intense or operates in a case in which the bone-marrow, on account of relative insufficiency, is not capable of this physiologic reaction, we see the formation of a megaloblastic marrow. This leads, it is true, to a regeneration of the blood, but in a way that is incomplete and different from the physiologic hematopoiesis of adults. 3. The reactionary power of the bone-marrow is extremely slight; there exists, as it were, a "torpor" of this organ which can not be aroused even by a severe anemia, so that the imperfect megaloblastic formation of blood fails to occur, much less a healthy reaction.

This gradual division, however, is not capable of standing close scrutiny, since the difference of the reaction, as far as the normoblasts and megaloblasts are concerned, depends not on the varying intensity, but on the qualitative difference of the anemic influence. The proof of this

[1] *Deutsch. Med. Wochenschr.*, 1900. [2] *Brit. Med. Jour.*, 1900.
[3] *Clinical Pathology of the Blood*, 1903.

is the occurrence of macrocytes and megalocytes in the blood of "mild cases"—*i. e.*, early stages, which is not at all conceivable without a megaloblastic degeneration of the bone-marrow. This peculiar metaplasia, therefore, can be produced by irritants of moderate intensity if they are of specific character.

That a preëxisting morbid condition of the bone-marrow is not to be made responsible for the megaloblastic reaction is in our opinion evident from the fact that the poison of the bothriocephalus is so frequently capable of producing the characteristic anatomic changes. The assumption would indeed be far fetched that a progressive pernicious anemia instead of a simple anemia arose in all these cases, simply because the bone-marrow of the affected individual was anomalous previous to the action of the worm poison. [It must be recalled, however, that certain cases of bothriocephalus invasion do not show anemia of progressive pernicious type. The possibility that in such cases the bone-marrow is capable of normal reaction must be admitted, though it has not been definitely proved.—Ed.]

Several difficulties are introduced by the third series of cases of severe anemia in which, as Ehrlich first recognised in vivo, every trace of reaction and transformation of the bone-marrow is wanting. Whether a deficiency of the marrow is entirely responsible, or whether special peculiarities of the specific irritants which make them capable of destroying the blood but not of stimulating a regeneration must be considered, can not at present be decided. Bettmann's investigations on the influence of arsenic on the bone-marrow of the rabbit contributes something to this question. By the administration of small amounts he was able to produce a transformation of fatty marrow into red, which simulated that of simple anemia; by employing larger doses this lymphoid metamorphosis occurred more slowly or not at all. This observation seems to show that a too intense irritant paralyzes the compensatory power of a bone-marrow which may be simulated by less severe irritations. A single case of bothriocephalus anemia, carefully observed both clinically and anatomically in which this "bone-marrow aplasia" (Ehrlich) was demonstrated, would be sufficient to decide this contested point. The question arises whether these rare cases which correspond clinically to Biermer's picture, but which lack the characteristics demanded by Ehrlich, as well as the anatomic alterations of the bone-marrow, are to be reckoned with progressive pernicious or severe simple anemia. If we were to proceed strictly logically, a special group should be made and we should speak of a normoblastic, a megaloblastic, and an "aplastic" anemia. Still, from a practical point of view, the

writers consider it more judicious to reckon these most rare cases with simple chronic anemia, to which they stand closest in their blood-picture. Whoever makes a careful morphologic analysis of the blood along the lines laid down by Ehrlich will always be able to separate them and draw the proper conclusions in regard to the prognosis.

[Engel[1] discusses the condition of the blood-making organs as indicated by the composition of the blood. He believes it is possible to establish the character of these organs by studying the blood. He distinguishes four types of bone-marrow and appends the character of blood met with in conjunction with these: (1) Normal marrow epiphyses contain red marrow, diaphyses, fatty marrow. In the former ortho- and polychromatic normoblasts may be found. In the blood, only normal orthochromatic erythrocytes. (2) "Insufficient" marrow (partly conjectural condition). Occasionally the nucleated cells in the marrow are as much increased in number as in pernicious anemia. The blood conditions associated with this are (*a*) chlorosis; (*b*) anemia or anemia with chlorosis; (*c*) the presence of pathologic red corpuscles in the blood. (3) Metaplastic marrow. Yellow marrow completely or largely converted into red marrow. In the red portions, megaloblasts and metrocytes and also, as in the blood, all transitional forms from normal to much enlarged nucleated and non-nucleated erythrocytes. (4) Aplastic marrow—rare. Epiphyseal marrow converted into fatty marrow. No nucleated red corpuscles nor leukocytes. The blood does not contain abnormal red cells, but the number decreases progressively.

In a paper read before the New York Medical Association[2] the editor expressed the view that pernicious anemia is undoubtedly a disease resulting from rapid destruction of the red corpuscles for the compensation of which the blood-making functions prove inadequate; and further, that the source of the hemolytic agents is the gastro-intestinal tract. He could not coincide with Ehrlich's view that there is a distinct perversion of bone-marrow function, but merely inadequacy.

This accords with the view of those, like F. P. Henry, who regard the marrow reaction of pernicious anemia as a reversion to embryonal conditions, even though there is some deviation of normal embryonal processes. In this connection the cases of metastatic carcinoma of the marrow with the clinical features of pernicious anemia ought to be recalled; as also cases described as sarcoma. Among those who have described cases of pernicious anemia (hematologically speaking) with sarcoma of the bone-marrow are Fede, Quincke, and P. Grawitz.—ED.]

As far as the distribution of the lympoid marrow is concerned we

[1] *Münch. Med. Woch.*, 1901, No. 4. [2] *Med. News*, Oct. 20, 1900.

may say that it is not rare to find normal fatty marrow in one tubular bone, while another shows the entire marrow transformed to red. From the post-mortem protocols the metamorphosis seems to affect the tibial marrow most frequently.

COURSE AND DURATION. TERMINATION AND PROGNOSIS.

Since progressive pernicious anemia is usually brought to the attention of the physician only after the symptoms are well developed, we must rely on the uncertain statements of the anamnesis for its beginning. Neither in cases with known etiology nor in those in which a simple anemia may be considered the forerunner, and naturally not in the kryptogenetic cases, can the time of the commencement of the disease be determined with absolute certainty. Only the cases which come on during pregnancy and after childbirth afford us more definite information.

The previous history of the patients is exactly alike in the majority of cases; they are very gradually attacked by a general weakness which renders it more and more difficult for them to continue their ordinary occupation. Work, whether physical or mental, which they were able to accomplish shortly before without difficulty, requires the greatest effort, and the strength gives out, especially when the work is prolonged. Simultaneously alterations in the appearance set in. The color of the face and hands becomes strikingly pale, the features become flabby, the eyes dull. Subjective disturbances are quickly added in the shape of paltipation, vertigo, tinnitus aurium, derangements of vision, and an inclination to fainting. Then further objective symptoms come on, among the first of which is slight edema.

The progressive character of the disease is shown by the steady increase of these symptoms despite rest and care, and the addition of other more severe ones which rouse the anxiety of the patient and his friends. The general decline in health and strength increases; the pallor takes on its peculiar character and rapidly reaches the highest grade; the edema becomes more marked so that it is apparent to the laity. The feeling of weakness is so great that the patient leaves his bed for only a short period daily or not at all, and he is completely incapable of bodily or mental effort. The cardiac disturbances increase on the slightest effort, on any bodily movement; in fact, a tormenting palpitation associated with dyspnea may set in spontaneously even during perfect quiet. Distressing symptoms on the part of the stomach and intestine very frequently appear. If the appetite was poor at the beginning of the disease, it decreases to a violent distaste

for every sort of nourishment; dysphagia, nausea, and vomiting set in; and frequently a diarrhea that can not be controlled by dietetic regulations is added.

These symptoms not rarely take on a paroxysmal character and present a picture which recalls that of severe acute intoxication.

Following these symptoms, or if they are wanting, the symptoms of progressive cachexia appear, unconsciousness develops, and leads to coma and death.

This general picture is subject to many alterations depending on special symptoms described in other sections, which lend variable characteristics to individual cases at different times, and to different cases in contrast with one another.

A very special peculiarity of progressive pernicious anemia which is scarcely ever encountered in such a marked degree in other severe chronic diseases, is the frequently mentioned interruptions in its course, the so-called **remissions**, or if one will, the paroxysmal-like occurrence of the disease. In any stage of the disease, even the most severe, a sudden change may take place independently of every treatment, resulting in a surprisingly rapid and complete restoration of the patient. This change occurs most frequently in connection with those gastric crises described previously. After the diarrhea and the violent vomiting have resisted every remedial effort for days, they suddenly cease; the patient, still extremely weak, experiences a feeling of well-being which produces in him the sensation of approaching recovery. The desire for food and drink is stimulated, becomes greater from day to day, and eventually even insatiable. The general strength increases with a rapidity otherwise seen only in youthful individuals after a severe infectious disease. Moreover, if the nutritive condition has suffered the loss of weight is quickly made up. An evidence of the rapidity and the degree of regeneration is furnished by the estimation of the red blood-corpuscles. In another section (see p. 257) was mentioned a case in which within seventeen days the number of erythrocytes rose from 1,340,000 to 4,115,000—*i. e.*, an increase of 163,000 per c.cm. pro die. Yet this is surpassed by cases of Laache and Schauman, in which an increase of 211,000 and 214,000 pro die respectively was found. As a matter of fact, only as many weeks are often necessary to bring the patient to blooming health, as it required months to produce the work of destruction.

Laache claims that precisely in the stage of regeneration progressive pernicious anemia is sharply differentiated from other anemic conditions. For while in simple anemia (see Curve, Fig. 5) the average "value"

of the corpuscles sinks on account of the increase of red blood-corpuscles poor in hemoglobin, in the early stage of regeneration of progressive pernicious anemia it is above the normal; in other words, in simple anemias the number of blood-corpuscles reaches the normal more quickly than the quantity of hemoglobin, while in progressive pernicious anemia both run parallel. Schauman and v. Willebrand, who recently confirmed this observation, see its explanation in the siderosis of the internal organs in progressive pernicious anemia, which makes it possible for the newly formed blood-corpuscles to obtain a larger amount of hemoglobin. A simpler explanation, however, is that at the beginning of the remission the bone-marrow has still at its disposal a large store of megalocytes rich in hemoglobin. Moreover, it is likely that the marrow, even after the removal of the hypothetic irritation which was the original cause of the formation of megaloblasts and megalocytes, still continues for a time to work in the old direction, and returns only gradually to the production of normal cells. Toward the end of regeneration the amount of hemoglobin in the corpuscles becomes normal or even sinks under the normal.

It was previously mentioned that a complete remission may occur quite apart from treatment, even when the patient is "in extremis." Laache observed a patient rouse from a five to six days' stupor and gradually return to perfect health; and Prof. Renvers has privately informed me of the case of a patient who was brought to the hospital "moribund," and who, without other than the symptomatic treatment demanded by her dangerous condition, aroused from the coma within twenty-four hours, and from that moment convalesced under the employment of arsenic till within a few months she was entirely well.

Moreover, in less advanced stages the disease may come to a sudden halt, and renounce for a time its progressive character or even entirely disappear. Further, this transformation may occur gradually without a crisis being evident. While dismissing from consideration at present the definite cure of bothriocephalus anemia, this stage of remission deserves special attention. The remission may be so complete that the patient feels "better than ever before," a feeling which is naturally in great part called forth by the remembrance of the suffering just past. Moreover, to the inexperienced glance of the laity, the recovery may seem to be complete. Still, on careful examination, signs are found which show that the recovery is not complete. For instance, an extreme excitability of the heart, in consequence of which insignificant influences increase the frequency of the pulse, persistence of the anemic

murmurs, an inclination, even though slight, to edema, and finally trifling anomalies in the composition of the blood.

In our opinion the greatest stress is to be laid on the last factor. The writers have several times been able to subject the blood of such cases to continuous control and have found the amount of hemoglobin and the histologic appearances practically normal; the few deviations in shape and size of the cells and their manner of taking the stain were so slight that they lay within normal limits. In fact, the only anomaly that the writers were able to find in this apparently normal blood was punctate erythrocytes. Though these were present in extremely small numbers, and not even in every preparation, they were found in every case several times (see Plate II., Fig. 4).

The further fate of these apparent recoveries shows better than these insignificant symptoms that, even in the stage of remission, the progressive pernicious anemia is only latent. After a more or less long interval the severe symptoms of the disease reappear and lead anew to an acme stage to which the patient succumbs, or an alternation of the two conditions may be repeated several times.

Not a few cases are reported in the literature in which the individual "paroxysms" are described from the first breaking out of the disease till death, and we take the liberty of referring to several:

Strümpell describes a case that showed its first symptom at the end of the year 1874 and the first severe condition in September, 1875, which resulted in perfect recovery after eight weeks. During the period from March to July, 1876, the status gravis was repeated. In November, 1876, the symptoms again became progressively worse till the exitus lethalis in April, 1877.

From their own experience the writers can report more frequent remissions in only 1 case. The disease began about September, 1894, and was severe in the middle of October of the same year. The patient left the hospital well at the end of November. Deterioration again set in in the spring of 1895 and complete recovery did not occur thereafter. In August, 1895, a renewal of the status gravis; in autumn of the same year the exitus lethalis (outside the hospital).

A case of Paechtner's showed repeated intervals, which were, in addition, very remarkable on account of their long duration: 1, Pretty severe condition July, 1888; 2, repeated June, 1889; then perfect health till April, 1894; death June, 1894.

Finally, we must mention a case quoted by Laache in a recent work from the Norwegian literature (Malthe, 1878); though unfortunately without stating the number of remissions or describing the blood-finding, so that it can not be determined with certainty from what time the disease should be reckoned with progressive pernicious anemia. The patient, who was a mason, was observed for ten years before death by Malthe, and during this time was so far cured "time after time" by Fowler's solution that he was able to continue his occupation.

In a case like Paechtner's, in which the patient remained well for almost five years, the assumption can not be disregarded that the disease was completely cured after the second paroxysm and that the attack in April, 1894, was a new one. Moreover, we can not disprove the view that the remissions represent actual cures which leave behind only an increased predisposition to the disease, as do, for instance, articular rheumatism, pneumonia, erysipelas, etc., though the scanty observations in regard to the behavior of the cases which escape severe paroxysms seem to speak against it. Decisive conclusions will be reached only when there is the opportunity to observe the patients continuously. A comparison with tuberculous disease seems more proper, for in this disease apparent recovery frequently occurs while a latent focus remains behind to break out again on trifling stimulus.

The literature contains numerous statements in regard to the entire *duration of the disease*. Sandoz mentions a case from Huguenin's clinic which proved fatal in fourteen days. During life ulcerative endocarditis was diagnosed and only on post mortem was the disease recognized as progressive pernicious anemia. Immermann and Eichhorst each report a case of six weeks' duration, though the commencement was characterized as only "rather sudden," in other words, it was not sharply determined. A case of H. Müller's, in which the disease began very acutely after a severe hemorrhage during parturition, proved fatal in seven weeks. In the majority of cases, as far as the beginning can be determined, the duration is under a half year. Between the beginning of the disease and death about five years occurred in cases reported by H. Müller, Laache, Paechtner, and about ten years in one observed by Malthe.

The fatal termination occurs in a large number of cases, in fact, in the great majority, after coma and a "vita minima" with complete loss of strength have been manifest for days. Some cases have been reported in which the end was ushered in by violent excitement, delirium, maniacal paroxysms or the reverse, marked depression or melancholia leading directly to coma.

In 1 case of Biermer's death occurred suddenly from cerebral apoplexy.

In almost every large work on progressive pernicious anemia we find a case of Litten's, reported in 1877, which terminated in medullary leukemia. In this case the post-mortem diagnosis of leukemia seems justified, yet, looking at the statements of the observer, the intra-vitam diagnosis of progressive pernicious anemia from the reported blood-findings is, to say the least, doubtful: "From the beginning—*i. e.*, eight days ante mortem—the number of leukocytes appeared somewhat increased"; there was no poikilocytosis and

a differential count of the individual leukocytes or a mention of erythroblasts (corresponding to the position of hematology at that time) was not made. Since this observation has been widely quoted, yet never confirmed by another case, the most natural assumption is that the case was one of leukemia from the start. The proportion of whites to reds is, as is well known, very variable, even in leukemia, and recent investigations show that it is readily influenced by intercurrent affections (see pages 133 and 134). On one day it may be 1 : 10, on the next 1 : 50, or even more, so that the diagnosis of leukemia is possible or can be excluded only by a differential count of the leukocytes.

A further frequently quoted observation of Laache's has likewise been made the premise for too far-reaching conclusions, though not by Laache himself. This relates to a patient with progressive pernicious anemia, who manifested several weeks before her death marked swelling of the lymph-glands and a small splenic tumor. The possibility of a transition of progressive pernicious anemia into pseudoleukemia was at once jumped at and a close relationship between the two diseases assumed. Since this case has remained the only one of its kind, there is good reason for thinking that it represents a coincidence of two different diseases. Moreover, this case comes from the period before the general employment of Ehrlich's blood methods.

In view of the above-cited communications in regard to asymptomatic intervals, which may last as long as five years, the criticism of the recoveries reported in the literature is evident.

The remark "discharged cured" is not a rare one in the literature; but in only an extraordinarily small number of cases do we find that the observer had the opportunity of seeing the patient after his discharge from the hospital. This being the case, the statement is wholly justified that the patient in question succumbed to a relapse. [Osler[1] refers to a case which came under observation in 1890 after a year's duration of the illness. He recovered and was discharged. In 1896 he was readmitted to the hospital with cancer of the stomach. In Pye Smith's article in the *Guy's Hospital Reports* 20 cases of recovery are mentioned. One of these cases treated and cured with arsenic in 1880 was found well by Colman in 1890. The editor has had 2 cases under observation more than five years after their cure and no recurrence had taken place.—ED.]

The statement that an actual cure took place should be made, according to our present experience, only when the patient remains free from a paroxysm for at least five years.

A case of Hayem's (observation V.) of a severe anemia post partum possibly responds to these demands. Hayem had the opportunity of seeing the patient several times up to five years after recovery and she presented no symptom of an anemia throughout this period. The diagnosis in this case is in our opinion by no means absolute. Megaloblasts were never found

[1] *Principles and Practice of Med.*

and the color index of the red blood-corpuscles was at the height of the disease only 0.90 to 0.79. Still numerous megalocytes were present and the clinical picture corresponded exactly to progressive pernicious anemia.

This case of Hayem's, if acknowledged to be progressive pernicious anemia, is the only one from the whole literature which can be given as an example of lasting recovery. Therefore the rarity of such an occurrence is so extreme that apart from bothriocephalus anemia we must designate the disease as *incurable.*

It is evident from what has been said in the different sections that we have no positive basis on which to make a **prognosis** as to the course of the disease, its probable duration, or the termination of any single attack. We can not foretell with certainty a fatal termination either from the clinical symptoms or from any extremely low percentage of blood-corpuscles; for the patient mentioned by Quincke, in whom the lowest number of corpuscles (143,000) ever seen in a living person was found, recovered completely. The morphologic examination of the blood likewise fails, for the writer has observed one patient recover from an attack which showed a large number of megaloblasts, complete absence of eosinophile cells, and marked leukopenia. Generally speaking it is true that the life of the patient is in greater danger the more intense the individual symptoms; for instance, the decrease of the blood-corpuscles to under a million, or of the hemoglobin to under 15 per cent., marked poikilocytosis, megaloblasts exclusively without normoblasts, a marked preponderance of megalocytes over the other forms, etc., are symptoms indicating a high degree of deterioration of the blood and give relatively a bad prognosis, though individual cases, as mentioned, may controvert all reckonings.

The occurrence of enormous numbers of megaloblasts and gigantoblasts together with numerous karyokinetic figures may possibly be of ominous significance. The few findings communicated so far have been in patients who succumbed to the disease one to two days later; still morphologic examinations of the blood from the decisive period are wanting in cases which were aroused from a deep coma and were at least relatively cured.

[Dock[1] states that at present we are not justified in ascribing to mitoses in the circulating erythroblasts any diagnostic or prognostic value.—Ed.]

The unfavorable prognostic significance of megaloblasts and of macrocytes in general is, therefore, only conditional, inasmuch as they only establish the diagnosis of a disease which is, according to our present knowledge, incurable.

[1] *Trans. Assoc. of Amer. Physicians*, 1902.

At the close of this section we have still a few words to say on bothriocephalus anemia, in which a causal therapy is capable of producing definite cure. Until the tapeworm is removed these cases run a course in no way different from the other forms of progressive pernicious anemia. Even the regeneration, according to Schauman, both as regards the increase of the red blood-corpuscles and of the hemoglobin, corresponds exactly with what has been described. On an average the daily increase in red blood-corpuscles in his cases amounted to 60,000 pro die, though in 1 case it reached the enormous number of 214,000. The rapidity of the increase in individual cases varied from day to day, and was usually greater at the beginning of convalescence than later.

On account of the fact that the hemoglobin did not increase in the same proportion as the number of red blood-corpuscles, the color-index quickly sank to normal or even under. Later on in convalescence the increase in both proceded hand in hand. The observations of Schauman in relation to the erythroblasts coincide fully with our previous description. Schauman completed these investigations by determining the average diameter. He found that at the beginning of the improvement the average increased, a fact which he is inclined to explain by the disappearance of the small forms, though undoubtedly the further maturing of the megaloblasts existing before the removal of the worm likewise plays a part. Moreover, Schauman himself observed an absolute increase of macrocytes in the blood following removal. Later on the average diameter becomes smaller and approaches the normal with the same rapidity that the macrocytes disappear from the blood.

When the symptoms of bothriocephalus anemia disappear after removal of the worm, we can undoubtedly speak of an absolute cure. Schauman had the opportunity of observing a small number of cases, for four and even eight years after the removal of the worm, and convincing himself that a complete restitutio ad integrum had resulted and persisted. In only one regard did a portion of those cured show a definite weakness, namely, in 10 out of 16 cases examined no hydrochloric acid was found in the gastric juice. From the conclusions arrived at in the discussion of achylia gastrica and its relation to progressive pernicious anemia (see p. 287), this may be explained by the assumption that in these cases a more or less high degree of anadenia developed simultaneously with the anemia, which was no longer curable. Mention has been made in another section that the general condition may be excellent in spite of the atrophy of the gastric mucous membrane.

Schauman's material gives only general and conditional data for the

prognosis of bothriocephalus anemia quo ad recovery, since a definite conclusion can not be drawn from the severity of the anemia. For cases which agree exactly as far as the blood examination is concerned, terminate sometimes in recovery, again in death. The prognosis is naturally relatively more unfavorable the more advanced the deterioration of the blood, for instance, the red blood-corpuscles under 1,000,000 or even 500,000.

COMPLICATIONS.

The complications occurring in progressive pernicious anemia are exceedingly rare and the disease apparently awakens no particular susceptibility to any other. At most the only suspicion which exists is that relative to the development of gastric carcinoma, which we mentioned previously.

It may be of importance to know that valvular defects, which are often erroneously diagnosed in progressive pernicious anemia, have been several times actually found at autopsy, for instance, a mitral insufficiency in 1 case of Schumann's and a complicated valvular defect in 1 case of Schauman's.

In comparison with other anemic conditions, progressive pernicious anemia shows only a very slight inclination to thrombosis formation in spite of the great feebleness of the heart, a circumstance which is to be explained by the diminished coagulability of the blood (Birch-Hirschfeld).

The occurrence of nephritis (Laache) is worthy of mention, since these two diseases show several features in common in their general pictures, especially albuminuria and edema.

It is remarkable that the disease rarely appears to pave the way for a tuberculosis, in spite of its not infrequent duration of several years. We have observed an example of the coincidence of these two diseases in Prof. Renver's ward. This was a case of general miliary tuberculosis of the lungs, in which the blood examination showed at the beginning of observation a severe progressive pernicious anemia. That the blood-finding was not to be referred to the tuberculosis is evident from the fact that this disease progressed to death within a few months, while the condition of the blood progressively improved.

In several cases of Laache's the occurrence of suppurative foci in different localities of the body has been noted. In 1 case there was a formation of multiple abscesses in the skin, in another a unilateral suppurative otitis.

DIAGNOSIS.

The diagnosis can sometimes be made from the first impression produced by the general appearance of the patient. The general clinical picture, which has been drawn more accurately in another section, presents several symptoms very characteristic on the first glance. The peculiar color of the skin, the intense pallor, the apathetic expression of countenance, and the frequent slight puffiness of the skin are often so conspicuous that they alone lead to the diagnosis. Naturally a careful examination should never be omitted, no matter how convincing the general appearance. Still, if on a thorough physical examination, it is found that the subcutaneous fat is well preserved, that the heart shows the clinical symptoms of a fatty degeneration, that the retina is riddled with hemorrhages, and that there is no severe disease of the internal organs, a conscientious physician can consider these grounds sufficient on which to base a diagnosis. For even to-day, during the period of hematology, we are able to recognize cases of progressive pernicious anemia reported from earlier times by the occurrence of these well-marked characteristics.

Nevertheless, when one of these cardinal symptoms is not evidently developed, or when a severe organic disease is discovered, sufficiently serious suspicions should be aroused to make an accurate examination of the blood indispensable. For we must realize that the diagnosis from the general disease-picture is too subjective a method to be of value in doubtful cases. Moreover every one of the special symptoms may be occasionally observed in simple anemias of severe grade. This is true of the incongruity between the condition of nutrition and the loss of strength, as well as of the fatty degeneration of the heart and of the retinal hemorrhages.

Still, whoever agrees with the definition of progressive pernicious anemia as a disease showing blood of a composition corresponding to the embryonal type, will naturally consider the examination of the blood indispensable, even in those cases in which the diagnosis is assured by the clinical examination. Moreover, in every case in which any gap is found in the clinical examination, the decision must rest entirely on the result of the blood examination.

In making a diagnosis the examination of the dried stained preparation is preferable to all other methods. According to Hayem and Laache it is possible by the estimation of the number of corpuscles, and of the percentage of hemoglobin and by the determination of the color-index, to separate progressive pernicious anemia sharply from other anemias, yet this is accomplished only by several different exam-

inations, requires costly apparatus, is very tedious, and requires constant practice. [The methods referred to are so constantly employed by careful practitioners that this criticism seems strained.—ED.]

In the examination of the dried stained preparation attention is first directed to the *diameter of the red blood-corpuscles.* The inexperienced will do well to have at hand for comparison a preparation of normal blood, though with practice it is easy to recognize without comparison and without a micrometer whether the diameter of the individual blood-discs is larger than normal. If only isolated red blood-corpuscles exceed the normal size the finding may be neglected; but if a larger number, for instance, one-fourth of the entire number, exceed the normal, this indicates an anomaly of blood formation. True, there is another condition in which macrocytes may be found in the blood, namely (according to v. Limbeck), in icterus; and Gram and Engelson contend that the enlargement in this disorder may be quite considerable. When icterus exists, therefore, great caution should be exercised in determining the significance of the megalocytes. Still, if the enlargement is marked and affects a large number, if forms of once and a half or double the diameter of the normal occur, and more than half of all the discs are affected, the diagnosis of progressive pernicious anemia is practically positive, since the only explanation for the occurrences of so many very large non-nucleated discs in the blood is their origin from megaloblasts, of the presence of which in the bone-marrow they are, therefore, a direct proof. [Capps has suggested determining the "volume-index" of the red corpuscles by enumerating the red corpuscles, and determining the bulk of corpuscles with the hematocrit. If, for example, the bulk exceeds one-fifth the normal bulk when the count is 1,000,000 (one-fifth normal), the volume-index is high. He found such a high volume-index regularly in exacerbations of the disease.—ED.] The finding of microcytes or of a considerable alteration in shape is a feature of every severe simple anemia, and is consequently of no value in the diagnosis.

Since, however, errors may arise as to the relative size of the red blood-corpuscles on account of certain technical imperfections in the preparation of the specimen (see page 26), the finding of *megaloblasts* becomes of the greatest importance. The principal significance of these cells lies in their presence in the bone-marrow, and this is sufficiently demonstrated by the appearance of their non-nucleated derivatives in the blood, still diagnostic errors are more surely avoided when the megaloblasts themselves are found in the blood. Mention has several times been made that their demonstration in the circulation fre-

quently requires considerable patience. The negative result of an examination is the only reason for a repetition within a short period, and the absence of megaloblasts should he stated with certainty only when they are not found in several preparations examined preferably on several consecutive days.

The positive finding of undoubted megaloblasts in association with numbers of megalocytes is pathognomonic for progressive pernicious anemia since they show indisputably that the formation of blood, at least in parts of the bone-marrow, is following the embryonal type, which is pathologic for adults.

How the occurrence of isolated megaloblasts found by a few investigators in other diseases, for instance, chlorosis (Hammerschlag), is to be explained, is still an unsolved question. That even in these cases it indicates a special peculiarity, is evident from the fact that among so many blood examinations as are at present undertaken in hospitals it is so rarely found. The most natural explanation is that these cases represent the beginning of a true progressive pernicious anemia; the only further fate of these patients could decide this. It is also conceivable that a specific irritation is sufficiently strong to produce a megaloblastic degeneration in a small area of the bone-marrow, which, with the removal of the irritation, proceeds no farther and retrogresses.

When megaloblasts are not found on repeated examination of the blood, the diagnosis of progressive pernicious anemia, based on the clinical symptoms, does not necessarily fall to the ground. As explained above, the diagnosis in this case may be made from the non-nucleated red blood-corpuscles. A blood of pronounced megalocytic character is characteristic of progressive pernicious anemia, even without megaloblasts. If, on the contrary, the blood contains only small forms poor in hemoglobin or a majority of such corpuscles (see Plate I., Fig. 2), the anemia must be reckoned among the simple anemias. Moreover, when the examination for megaloblasts is negative, we must be mindful of the fluctuations affecting the blood in the course of the disease, for a short time after a negative finding an examination may prove positive.

[Referring to the diagnosis of pernicious anemia, Lipowski[1] states that megaloblasts are not infrequently absent from the blood. He reports an instance in which the hemoglobin fell to 10 per cent. and the red corpuscles to 800,000, and in which there were hemorrhages from the skin, changes in the eye grounds, and irregular fever, but at no

[1] *Deutsch. Med. Woch.*, May 24, 1900.

time were morphologic changes in the corpuscles observed, excepting some change in size very late in the disease.

William Pasteur[1] communicated to the Clinical Society of London a case of pernicious anemia in a man aged twenty-four, who had left his work three weeks before on account of weakness and breathlessness. He was extremely anemic. The spleen was not enlarged. He was suffering from double hemorrhagic neuroretinitis. His sight had gradually failed. There was moderate fever. The blood showed marked oligocythemia without high color-index. The leukocytes numbered 2600, there being a relative lymphocytosis; no megaloblasts or poikilocytes could be found in the blood. The autopsy showed marked iron reaction in the liver, and a slight reaction in the spleen and testis. The chemic reaction showed six times the average amount of iron in the liver. The marked and rapid hemolysis led him to classify the case as one of pernicious anemia. The absence of characteristic changes in the blood was the important feature.

R. C. Cabot[2] states that megaloblasts predominated at the final examination in 37 cases, but were absent in 3 cases, in which only one examination was made.—ED.]

The occurrence of *normoblasts* carries no weight in the diagnosis. The simultaneous presence of megaloblasts and normoblasts gives no reason for doubting the diagnosis, since it merely shows that the megaloblastic degeneration does not affect the entire bone-marrow. Still, from a number of observations, we are able to draw the conclusion that the occurrence of normoblasts in large numbers is sometimes the forerunner of a beginning remission.

The *white blood-corpuscles* play an insignificant rôle in the diagnosis. In order to make them of value in the diagnosis it is necessary to repeat the examination, because the leukopenia ordinarily seen in progressive pernicious anemia may at any time be wanting, owing to accidental complications, and in the same way the more or less marked hyperleukocytosis usually present in simple anemia may show fluctuations which can lead to error. In those cases of Ehrlich and others in which, in spite of a severe anemia, a metaplasia of the bone-marrow did not take place ("aplastic anemia"), the persistent leukopenia decided the diagnosis. It was shown that the leukopenia (relation of whites to reds 1 : 1000; red blood-corpuscles 213,360) was produced by the absence of the bone-marrow cells, so that only 14 per cent. of polynuclear neutrophiles were present, while eosinophiles and nucleated red blood-corpuscles were entirely wanting. On this account Ehrlich con-

[1] *Lancet*, Nov. 21, 1903. [2] *American Jour. of Med. Sciences*, August, 1900.

tended, and his view was confirmed by autopsy, that there was no transformation of fatty into red marrow; in other words, that this was not a case of genuine progressive pernicious anemia.

The cases of metastatic tumors (carcinoma, sarcoma) in the bone-marrow (E. Lazarus, Epstein), which strictly can not be reckoned with progressive pernicious anemia, are clinically differentiated from it with difficulty, though characteristic differences in the blood-cells will indicate the proper diagnosis. In contrast to progressive pernicious anemia, the cases in question showed a considerable increase in leukocytes, so that the proportion of whites to reds was 1 : 50, even 1 : 25. Moreover, from Epstein's report, it is evident that in his patient there was not only a marked polynuclear hyperleukocytosis, but even numerous neutrophile and eosinophile myelocytes in the blood. Further, the number of nucleated red blood-corpuscles was much greater in these two observations than is usual in progressive pernicious anemia. (In contrast to this, several cases of bone-marrow tumors have been described—Nothnagel, Ehrlich, E. Grawitz)—which ran their course without special morphologic alterations in the blood; in fact, rather under the picture of a severe simple anemia or that of an "aplastic" anemia.)

[Thomas Houston[1] has published some very interesting observations relating to the conditions that simulate pernicious anemia. First of all he reports a case of generalized secondary carcinoma invading the bone-marrow among other structures, in which the morphology of the blood, the clinical symptoms, and the state of certain parts of the bone-marrow simulated exactly the conditions found in typical pernicious anemia. He enters into detail regarding the blood, especially with regard to the high color-index and the presence of megaloblasts, and shows how exactly this case corresponds with pernicious anemia. The pathologic examination did not show the hematogenous iron-pigmentation met with in pernicious anemia, but this, he thinks, might be explained by the extensive cancerous invasion and the consequent destruction of liver function.

Leaving this case out of consideration, the author states that his experience affords no justification for the view that has been held that it is impossible to differentiate between the blood of pernicious anemia and certain grave secondary anemias. He tabulates over 150 cases with hemoglobin below 50 per cent., including a number of cases of pernicious anemia and various forms of secondary anemias. Only 1 of the cases of pernicious anemia showed a color-index below 1.0, the figures being 0.96, and only 1 case not pernicious anemia (the case before referred to) an index above 1.0.

[1] *British Med. Jour.*, November 13, 1903.

Among the conditions said to simulate pernicious anemia are hemorrhage, intestinal parasites, pregnancy, and cancer. With regard to hemorrhage, he opposes the view of Stockman very earnestly, and shows that the blood-condition after hemorrhage is essentially a chlorotic one, without a megaloblastic character. He contends that the criteria for the diagnosis of pernicious anemia used by Stockman in the interpretation of some of his cases are unreliable. With regard to parasites, and especially anchylostoma, he holds that the color-index is low and eosinophilia is common, conditions not found in pernicious anemia. He quotes Ehrlich's admission that bothriocephalus anemia may be identical with pernicious anemia, and it may be assumed that he accepts this with Ehrlich's explanation that there is a specific toxic irritation of the bone-marrow. With regard to pregnancy, Houston found that all of his cases of severe anemia were of the secondary type. He quotes Ewing and Ahlfeld, each of whom states that in a large experience no case of pernicious anemia has been found associated with pregnancy. Finally, Houston tabulates a number of cases of cancer with marked anemia to show that such cases do not show the condition of the blood seen in pernicious anemia. When, exceptionally, such characters are seen, it is, he thinks, due to malignant deposits in the bone-marrow.—ED.]

The other physical and clinical methods of examination of the blood are of no value in the diagnosis. The observations are still too scanty to draw diagnostic conclusions from the diminution of the coagulability of the blood as demonstrated by Hayem and his pupils.

If the diagnosis of progressive pernicious anemia has been made by the clinical and hematologic examination, an accurate and frequently repeated macroscopic and microscopic *examination of the feces* should be made in order to determine the presence of tapeworm segments or eggs. If this examination is repeatedly negative and the strength of the patient allows, an anthelmintic should be given in order to render the diagnosis secure and perhaps bring about recovery at the same time.

Differential Diagnosis.—Since we have now learned the data on which to make a diagnosis in doubtful cases, it is sufficient to indicate briefly the conditions which may be clinically confused with progressive pernicious anemia:

1. Different forms of acute and subacute *endocarditis*. The subjective and objective symptoms on the part of the heart are often so pronounced in severe cases of progressive pernicious anemia that they may readily mislead to the diagnosis of endocarditis. The intensity of the murmurs especially is frequently such as to occasion surprise on

the discovery of a negative postmortem finding or the cessation of the symptoms with the setting in of a remission. The difficulties of the physical diagnosis are increased by the fact that progressive pernicious anemia may be associated with hydropericardium and high fever, and that on the other hand septic endocarditis as well as other septic processes may lead to severe anemia (Fischl and Adler). Eichhorst was justified in his statement from the standpoint of hematology at the time of his monograph that the differential diagnosis between acute endocarditis and progressive pernicious anemia "may present unconquerable difficulties."

2. The clinical differentiation of a progressive pernicious anemia from a concealed *gastric carcinoma* may likewise present unconquerable difficulties. The gradual increase in cachexia, obstinate anorexia, intense nausea, dysphagia, vomiting, hematemesis, the sensitiveness of the gastric region to pressure, and the persistent absence of free hydrochloric acid are symptoms common to both. If the examination of the blood shows undoubtedly the presence of a simple anemia, the diagnosis of carcinoma is assured, but if the composition of the blood is that of progressive pernicious anemia, the presence of a carcinoma ventriculi is not excluded, as has been shown in the special symptomatology (p. 243).

3. Occasionally the spinal symptoms are so prominent that the disease may be mistaken for a pure *spinal affection.* It is, therefore, advisable to control every case of spinal disease associated with anemia by a careful examination of the blood.

4. Subacute cases of progessive pernicious anemia which came under the eyes of the physician only when well developed have given rise to confusion with *typhoid fever* (Biermer) and *meningitis* (Laache) on account of the severe general symptoms, the stupor, the high fever, and the diarrhea.

5. The occasionally observed bronzing of the skin (see p. 263) may lead to confusion with Addison's disease.

6. Finally, we must mention Eichhorst's rare finding of a hemorrhagic hydrothorax in several cases of progressive pernicious anemia, since this is ordinarily considered pathognomonic of a thoracic neoplasm.

THERAPY.

CAUSAL TREATMENT.

No treatment of progressive pernicious anemia directed against its cause has as yet been found except for the forms produced by intestinal parasites, especially the Bothriocephalus latus. As a matter of fact,

the removal of the worm in these cases first demonstrated that the parasite was responsible for the disease.

Extract of felix mas in its ordinary doses (2–4 gm.) should, as a rule, be administered at once after the diagnosis of progressive pernicious anemia and the presence of tapeworm eggs or segments has been determined. Still, in cases which come into the hands of the physician in a condition of intense weakness with severe gastric symptoms, uncontrollable vomiting, and obstinate diarrhea, symptomatic treatment is necessary before the remedy, which is very severe even in health, is administered.

According to Schapiro and Schauman the administration of the extract of felix mas is frequently followed even in previously apyretic cases by a considerable rise of temperature. In a case described by Schapiro the fever rose gradually till it reached 40 to 40.5° F. on the fifth day, on the following day it fell by crisis, and thereafter the curve remained normal. In Schauman's cases, in which a fever already existed, the temperature did not sink immediately after the removal of the worm, but remained elevated for several days to two weeks; in 1 case, to one and a half months. In general, the convalescence and the regeneration of the blood showed a course similar to that described in remissions.

The comparative harmlessness of this treatment makes it advisable to use it even in cases of progressive pernicious anemia in which eggs or segments have not been found as soon as the strength of the patient and the condition of the gastro-intestinal canal allows it. A negative history should not prevent this treatment; infection with Bothriocephalus latus may at the present day occur in any locality, even though the patient never visited a particularly predisposed district. In fact, only lately the transportation of sea-fish, to which is frequently ascribed a rôle in the infection, has taken on extraordinary dimensions.

The treatment may be considered causal when it is directed to remove or render harmless the hypothetic toxins thought to be produced in the intestinal canal and exercise a hemolytic effect.

Such an attempt was first reported by Jürgensen, who administered extract felix mas in a severe case with the result that a rapid improvement set in, though nothing like a tapeworm was at any time found in the stools. Jürgensen attributed the improvement to the energetic evacuation of the intestine and the removal of enormous numbers of "bacterium termo." Sandoz observed "recovery" in a case of progressive pernicious anemia after repeated washing out of the stomach. Dieballa ascribes complete disappearance of the anemia

in 1 of his cases to large doses of salol (5 gm. pro die). He had treated this case without result by a series of other methods recommended for progressive pernicious anemia. He represents the action of the salol as similar to that for which it is recommended in cholera, namely, after breaking up into phenol and salicylic acid, it suppresses by its disinfecting properties abnormal intestinal fermentation. Dieballa's hypothesis is deprived of every theoretic foundation by the exact investigations which have shown the impossibility of disinfection of the intestinal canal (Stern). The improvement of his patient, therefore, must be referred to other factors than the salol. In case constipation exists, however, an evacuating treatment should be tried, though it is not necessary to employ the energetic and undoubtedly harmful measures of Jürgensen and Sandoz, but only a regular and thorough evacuation by mineral waters, salts, or clysters continued over some time. It has been demonstrated that at least the number of bacteria in the feces can be more readily reduced by this treatment than by the employment of agents which show disinfecting properties in the test-tube. Moreover, it is well known that abnormal decomposition in the intestine can be effectually controlled by dietetic regulations, and later on we shall see that in progressive pernicious anemia in particular this method can be employed with the greatest advantage.

[Acting upon Hunter's hypothesis that the disease is a streptococcus infection, several investigators have tried the effect of antistreptococcus serum (McPhedran, Walsh, and others), but the results are uniformly disappointing. Various forms of mouth-washes and intestinal antiseptics have been tried on the same hypothesis. Hunter's suggestions for treatment were: (1) Antisepsis of the mouth; (2) gastro-intestinal antisepsis; (3) administration of arsenic; and (4) antistreptococcus serum.—ED.]

Organotherapy.—Some investigators, guided by the results of organotherapy in other diseases, have tried it in progressive pernicious anemia, proceeding on the assumption that the disease takes its origin in the bone-marrow. In administering marrow they have sought a causal therapy. The literature contains reports of such treatment from Frazer, Barrs, Drummond, Pepper and Stengel, Grawitz, and others. The last-named authority observed absolutely no result from its administration, while the others attribute to it the recoveries in several of their cases.

In the majority of cases the marrow was given fresh or in a glycerin extract, and it was found that after a short time patients usually manifested a decided distaste for it. Barrs, therefore, has offered a prepara-

tion which was administered and well borne for months in a daily dose of about 90 gm. His recipe is as follows: 90 gm. fresh red marrow is beaten up to a paste with about 30 gm. port wine, 30 gm. glycerin, and about 20 gm. gelatin; the marrow is mixed with the wine and the liquefied gelatin with the glycerin in two hot mortars and the two mixtures poured together.

From the observations so far made a decision can not be reached as to the therapeutic effect of the bone-marrow, especially since in several of the reported cases it was given only in conjunction with arsenic or something else. Those who refuse to accept the theory that progressive pernicious anemia is myelogenous in character, see in the administration of bone-marrow only a treatment, and not a very energetic one, with iron or hemoglobin.

We must finally mention Gusserow's causal treatment of the progressive pernicious anemia of pregnancy by the induction of premature labor; its complete failure has prevented obstetricians from further attempts.

TREATMENT BY THE TRANSFUSION OF BLOOD.

Years ago Gusserow made the attempt to combat the severe symptoms in certain cases by the transfusion of blood, but without success. Later a whole series of other clinicians tried the same, but in vain, till Quincke succeeded in obtaining marked improvement in 1 case. This case is the one, several times quoted, in which Quincke found that the number of red blood-corpuscles sank to 143,000 per c.mm. The intra-arterial transfusion of 85 c.cm. of defibrinated human blood was followed in twenty-four hours by an evident change in the general condition, and a complete restoration of the patient within several months.

From the numerous communications on this subject in which reports of success and failure alternate with one another (compare Haarth), the writer will mention only that of Ewald, because in none of the other patients was the danger of death so threatening. Ewald, without any hope of success, but only desirous of leaving no stone unturned, made an intravenous transfusion of 85 c.cm. of defibrinated blood in a patient who lay in the deepest coma with reflexes practically abolished. The first result was manifest on the following day in a return of the reflexes and consciousness, and with astonishing rapidity the patient recuperated so as to be able to make a journey after several months. On the occurrence of a relapse, about six months later, the transfusion of 300 c.cm. of defibrinated blood was completely without effect.

Immediate effects of the transfusion were manifest in almost all cases in marked anxiety, dyspnea, chill, and elevation of temperature to 39° or 40° F. All these symptoms disappeared after a few hours.

The hemoglobinuria and nephritis observed by Quincke immediately after the transfusion likewise disappeared completely within a short time.

To these 2 cases we should like to add Haarth's statistics of 39 cases, in which the result was positive in 17, inasmuch as a temporary improvement occurred immediately after. Among the cases showing negative results, there were a great number in which, as in Ewald's case, the transfusion was tried only as a last resort, or in which other severe complications were present.

In consideration of these facts, it is in the writer's opinion impossible to doubt the influence of the transfusion of blood. But one must be mindful of the change which frequently occurs spontaneously, or after simple symptomatic therapy in equally severe cases (compare Renver's case, p. 302), and must recognize that the administration of the treatment and the beginning of the remission may occur at the same time, purely as a coincidence.

When we look for an explanation of the favorable effect of the blood transfusion, no satisfactory one can be found. To attribute the result to the introduction of living blood, on the supposition that it is capable of taking up a part of the physiologic function (Eichhorst, Quincke), is not compatible with the fact that extremely small quantities of blood have been found sufficient. Ewald injected 85 c.cm., Quincke in 1 case only 50 c.cm., and Oré saw the symptoms of a severe pregnancy anemia disappear within several weeks after the transfusion of 40 c.cm. Ewald suggests the hypothesis that the injected healthy blood acts as an antitoxin to an unknown poison circulating in the organism in progressive pernicious anemia.

With this lack of a theoretic foundation, what are the indications from the experiences so far reported for the employment of blood transfusion in progressive pernicious anemia? In cases which manifest a severe but not an immediately dangerous condition, other therapeutic measures should first be tried, especially arsensic. Only when these produce no result or their employment is impossible, and the disease symptoms are evidently progressive, transfusion is to be done. It is likewise indicated in all severe exacerbations, in threatening collapse, and naturally in coma. When done with care no objection can be raised against it. From the observations so far made, no injurious effect has been found apart from the transitory symptoms mentioned above. (For the technic of the operation, see p. 175).

REMEDIAL TREATMENT.

Arsenic.—Since Byrom Bramwell recommended the use of arsenic in progressive pernicious anemia in 1877, this remedy has been employed more than any other and has even acquired the reputation of a specific. With few exceptions, all writers unreservedly attribute the principal effect to arsenic in cases where improvement followed its employment. Padley was the first to show a series of comparative statistics in regard to the results of treatment with iron and other remedies on the one hand, and with arsenic on the other. Among 48 cases in the first group, 42 died, 2 were still under treatment, in 3 the result was not given, 1 was cured. Among 22 treated with arsenic, Padley observed 16 "recoveries," 2 improvements, 4 deaths; among 57 treated with arsenic Fürbringer reported 4 relatively cured, 16 improved, 10 unimproved, and 27 deaths.

Still, in spite of these statistics, we can not consider that the favorable influence of arsenic on progressive pernicious anemia is incontestible. For, in the first place, we find that the old literature before the introduction of arsenic describes surprising improvements "by no means rarely" (Eichhorst). In the second place, not a small number of cases have been reported in which the change from a deep coma occurred without the administration of arsenic (see p. 302). Finally, we have Schauman's observation that in 18 cases of bothriocephalus anemia treated with arsenic after the removal of the tapeworm, the regeneration of the blood was only slightly more rapid than in 12 treated without arsenic.

The favorable influence of arsenic seems to the writer to be less marked in these statistics than it actually is in the course of individual cases, especially during the stage of remission. We have mentioned in another place the general tendency to changes during the remissions, particularly in the blood-picture. For instance, we suddenly find a more marked poikilocytosis, isolated examples of megalocytes, more numerous punctate erythrocytes, etc. These anomalies disappear, as a rule, within a few days upon the administration of arsenic and the blood-picture becomes again practically normal. From these observations it would seem that arsenic is capable of suppressing the outbreak of a relapse. In this sense Laache thus expresses himself in reference to a case observed by Malthe: "Fowler's solution places the disease literally in our hands."

For a long time considerable doubt was thrown on the specific effect of arsenic by the fact that theoretic grounds for its curative action were wanting, especially after several investigators (Stierlin and others)

had shown that, on the contrary, it exercised a deleterious influence on the blood. The removal of this gap has been accomplished by the recent work of Bettmann, who directed his investigations to the nature of arsenic-poisoning and the alterations in the blood and bone-marrow produced by it. From these investigations we are able to draw more definite conclusions in regard to the therapeutic action of arsenic.

Bettmann showed by his experiments that toxic doses of arsenic produce a double effect: 1. The blood-corpuscles in the circulation become less resistant and are destroyed in larger numbers. 2. Young elements with undoubtedly increased resisting power are thrown into the circulation from the bone-marrow in numbers exceeding the normal. The larger the amount of arsenic, the greater the destruction, and the severer the anemia. From this we may draw the conclusion (the careful experimental confirmation of which would be very desirable) that on the administration of very small and gradually increased quantities of the poison, the damage to the corpuscles in the circulation is more than compensated for by the production of new blood-corpuscles. An intimation of the curative power is evident from Bettmann's experiments on the effect of arsenic in animals made anemic by previous treatment with arsenic. In this case the number of corpuscles temporarily increased and the proportions of individual leukocytes temporarily approached the normal.

The treatment of progressive pernicious anemia with arsenic as heretofore practised continues, therefore, to hold the first place. In regard to its practical employment in this disease the same rules apply as in its administration generally, especially the regulation of a gradual increase in dose. We begin with very small quantities, 1 mg. pro die of arsenious acid, in doses of 0.5 mg., and increase about 0.5 in two to three days, in other words, to 1.5 mg. Reasonably small doses are almost always successful and the maximum officinal dose need scarcely ever be employed. When the drug is well borne and has produced improvement, it is recommended to continue the remedy at the highest dose reached for several weeks, and then lessen it gradually in the manner that it was increased. Even during complete remission it is advisable to administer the arsenic now and then in the same way for six to eight weeks. The general rule must also not be forgotten never to give preparations of arsenic on an empty stomach.

In order to accomplish the gradual increase, administration in liquid form is usually recommended. The preparation almost always employed is Fowler's solution, 16 drops of which contains 0.01 gm. arsenious acid. Ziemssen recommends the subcutaneous injection of liq. sodii

arseniosi; by using this both the digestive disturbances and the local caustic effect occurring after the injection of the potassium salt are more or less avoided. In the beginning he injects once daily 0.25 c.cm. of a 1 per cent. solution of the sodium salt and increases gradually sodii arseniosi, corresponds to the maximum dose of Fowler's solution to 2 c.cm. pro die administered in two doses; this quantity = 0.02 pro die.

In addition, especially for long administration, drinking-water containing arsenic has been recommended. According to v. Noorden the following corresponds to 1 mg. arsenious acid:

Roncegno water	8 c.cm.
Strong Levico water	115 "
Guberquelle	165 "
Weak Levico water	1050 "

A serious, often absolute objection to arsenic, is its allied effects, which consist in a hyperesthesia of the mucous membrane of the mouth, a sensation of irritation in the esophagus, and severe disturbances of digestion—namely, anorexia, cardialgia, nausea, diarrhea—symptoms which are peculiar to progressive pernicious anemia apart from the employment of arsenic. These symptoms demand the unconditional cessation of the drug. Another symptom, edema of the eyelids and extremities, which is attributable to the chronic action of arsenic, is likewise seen in progressive pernicious anemia. On the appearance of such a symptom the arsenic treatment must be stopped for a time in order to decide whether it is responsible.

Recently cacodylic acid, an organic arsenic combination, and sodium cacodylate have been recommended as very effective substitutes, which are free from the untoward effects of arsenic. According to Podalowski, Prochorow was the first to observe the striking tonic effect of this drug in phthisic patients. Gautier observed very good results from the drug among others in anemic cases, and found it was borne in large doses over long periods. I know so far of no communications in regard to its effect in the treatment of progressive pernicious anemia.

As to the method of employment, Gautier prefers the subcutaneous injection in the following formula:

Acid. cacodylic		5.0 parts.
Natr. bicarb.	q. s. ad saturat.	
Cocain. hydrochl.	ad.	0.8 "
Creosot.	gtt.	5.0 "
Aq. dest.	ad.	100.0 "

Of this Gautier injects 1 c.cm. daily; after a week he allows an interval of a week, and continues the administration in this wise for months.

Iron.—Treatment by iron, which failed so signally in the hands of the older physicians, is no longer practised during the severe stage of the disease. The richness of the erythrocytes in hemoglobin and the large quantities of iron stored up in the organs show that there is no deficiency which might demand its administration.

After the remission has set in, iron is sometimes administered for the purpose of increasing the hemoglobin when it has not yet reached the normal, or in general as a tonic. Still, Litten claims that he has seen actual injury result from its employment in this disease.

Phosphorus and **quinin**, which were tried by several investigators before the introduction of arsenic, are mentioned only for the sake of the historic interest.

Honigmann tried **inhalations of oxygen** in several cases of severe simple and progressive pernicious anemia. A decided improvement was noticed in only one patient. The fact that advance in technic has lessened the trouble and the cost of oxygen inhalations may lead to new attempts with it.

DIETETIC AND CLIMATIC TREATMENT.

The most important prescription regarding the general manner of living is complete rest. In severe stages of the disease the patient is constrained to avoid every effort by the intense muscular weakness, but with improvement, like convalescents generally, he readily overestimates his strength; even during remissions he should confine his exertions within the limits of fatigue. Every effort exceeding this moderation is revenged by new or increased disturbances of the heart, and is followed by a general exhaustion that yields only gradually.

The same advice of rest is applicable to intellectual work; moreover, every mental excitement must as far as possible be eschewed.

The patients possess a very slight power of resistance to extremes of temperature; they become cold very easily and must consequently be protected by special room temperatures or corresponding clothing; they likewise bear high temperatures very badly and should avoid being exposed to them.

A climatic treatment may be considered in the case of more resistant patients. So far we have no communications relative to the effect of high altitudes on the composition of the blood in this disease. Nevertheless, the proof that an increased blood production takes place under the influence of high altitudes may be looked on as established, and this is a sufficient reason for bringing suitable cases, especially during the hot season, to moderate altitudes, for instance, 800 to 1000 m.

The rapid relaxation which patients experience in high temperatures make Southern climates apparently unsuitable. The resisting power necessary to withstand stormy weather forbids sojourn at the sea.

A regular general massage of the body seemed to the writers very beneficial in several patients during long remissions. It counteracts the enforced inactivity of the muscles and is to be decidedly recommended when an inclination to edema exists.

The nutrition of the patient is often exceedingly difficult; in severe cases the vomiting and the absolute distaste for every kind of food may render it impossible to give any nourishment in quantities worthy of consideration. For a time after the vomiting ceases we must be extremely cautious and limit ourselves to the frequent administration of small amounts of liquid nourishment. As a rule, milk or mixtures of milk with coffee, tea or cocoa, and grits, rice and vegetable soups are borne best; strong irritants like alcohol, strong infusions of tea or coffee or even concentrated bouillon, are not borne at all. Solid food is to be introduced into the menu very gradually, just as in other severe gastro-intestinal affections.

A very frequent symptom, even during advanced convalescence, is a marked distaste for meat. We can and must reckon on this and limit the patient to a vegetable diet; as a matter of fact, this has recently been strongly recommended in anemic conditions. When vegetable nourishment has been carried out for several weeks, and this readily meets the demands of the body on account of the avoidance of exercise, the patient usually expresses the spontaneous wish to have meat added to his meals.

According to Neusser this temporary vegetable diet is the best means of combating the increased intestinal decomposition, so that in some cases we are perhaps actually administering a causal therapy.

The treatment of special accidents, for instance, collapse, differs in no way from the same in other conditions.

THE NATURE OF PROGRESSIVE PERNICIOUS ANEMIA.

In the individual sections on the etiology, the pathogenesis, the symptomatology, and the pathologic anatomy of progressive pernicious anemia, the question of its nature has been frequently discussed. In making the attempt to explain exactly the nature and the origin of the pathologic changes from the material at hand, we must not forget what was said in the introduction, that anemias only arise from (*a*) a defective blood formation, (*b*) an increase in blood destruction, or (*c*) a coincidence of both.

We have learned to recognize as the most important characteristic of progressive pernicious anemia a severe disturbance of blood formation expressed by a megaloblastic degeneration of the bone-marrow, and we have, therefore, associated the nature of the disease especially with this anomaly.

An increased destruction of red blood-corpuscles is shown by the almost unexceptional abnormally marked urobilinuria during life and the siderosis of the different organs post mortem. Whether the absence of siderosis in a few rare cases indicates that an increased destruction did not take place or whether the products of destruction had been used in another way in a later stage, can not be decided. Still, the assumption can not be denied that in a few cases of progressive pernicious anemia an increased destruction of blood failed to take place.

What significance have these two observations in the pathogenesis of progressive pernicious anemia? Are we justified in seeing in one, that is, either in the degeneration of the bone-marrow or in the increased blood destruction, the origin of the symptoms peculiar to the disease? We shall be least likely to fall into serious error if, before answering this question, we first take up that form of progressive pernicious anemia the etiology of which we know, the pathogenesis of which we understand pretty well, and the whole symptomatology of which is familiar to every investigator.

We have seen that we are justified in attributing to the Bothriocephalus latus a specific poison capable of causing an outspoken progressive pernicious anemia. To attribute to this poison a blood-destroying action is not sufficient to explain its causation of this particular form of anemia, for clinical observation and experiments teach us that long-continued blood destruction, sufficient even to endanger life, leads in the great majority of cases not to progressive pernicious anemia, but only to a very severe simple anemia. When, therefore, we find that a disturbance of blood formation is added to the increased destruction, this also must be attributed directly to the influence of the bothriocephalus toxin, in other words, the anomalous formation and the increased destruction are coördinate effects of the same cause. Moreover, we can conceive from the analogy of arsenic-poisoning that the bothriocephalus toxin may under particular circumstances exercise only one of these two effects. This is supported by the fact that we have learned to recognize further changes in the body which can only be regarded as the direct result of the poison and not of the anemia, namely, the atrophy of the gastric and intestinal mucous membrane and the degenerations of the central

nervous system. These do not occur regularly in every case, but in one we see one lesion, in a second another, in a third both together, and in still others none of them. Whether certain modifications of the poison or a particular predisposition of the organs in question, namely, the blood, bone-marrow, gastro-intestinal mucous membrane, and nervous tissue are responsible for these differences, we are not prepared to state.

Is it now permissible to apply the reasoning evident in the case of bothriocephalus anemia to other forms of progressive pernicious anemia? In the solution of this problem experimentation fails us completely. By frequent bleeding, inanition, infection, and intoxication, we are able to produce anemias of the severest kinds, but the picture always remains one of simple anemia. Even with the specific blood-toxins which directly destroy the corpuscles in the circulation, we can only produce conditions which show a combination of simple anemia and hemoglobinemia, in that they are characterized by normocytes, microcytes, normoblasts, and hemoglobinemic inclusions. When, therefore, cases of progressive pernicious anemia occur that are undoubtedly attributable to these causes, we must confess ignorance of the factor which produces this transformation of a simple to a progressive pernicious anemia.

We are still less in a position to explain the pathogenesis of the kryptogenetic cases. The best-known theories (Hunter, Silbermann, Stockman) all attribute their origin to an increased destruction of blood, and are differentiated from one another by the way that this is brought about. It is evident, however, from our previous discussion that this would explain only a single symptom, not the general characteristics of progressive pernicious anemia.

Moreover, there is no positive proof of the interdependence of the abnormal blood formation and the increased blood destruction on one another in the sense that less resistent elements are produced which succumb more readily.

For these reasons and on account of the analogy with the much more apparent conditions in bothriocephalus anemia, we incline to the conclusion that the megaloblastic degeneration of the bone-marrow, the most important characteristic of progressive pernicious anemia, is neither the cause nor the effect of the increased blood destruction, but that both are the result of a common cause. As long as we have no other explanation for the origin of this megaloblastic degeneration, we will consider the cause a toxin having a specific action on the bone-marrow. There are undoubtedly a large number of such toxins, as we have attempted to show in the section on Pathogenesis, and the differences

in the manner of origin, as well as in the symptoms in different cases, are most readily explained by the varying action of different toxins to which only the one property of causing a megaloblastic degeneration of the bone-marrow is common.

In representing the results of the megaloblastic degeneration of the bone-marrow, we must remember the differences stated in different sections between megaloblastic and normoblastic formation of blood. According to Ehrlich the former is a highly defective process which lacks the power of compensating for the loss in blood elements. The result is that all the symptoms of simple anemia become especially intense, and in this lies the pernicious character of the disease.

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CHLOROSIS.

BY

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22

CHLOROSIS.

DEFINITION.

A DEFINITION should not refer to the symptoms, but to the nature of the disease in question. Our position in reference to chlorosis is difficult, since we are still absolutely ignorant of the character of the affection and any attempted accuracy of definition would meet with some contradiction. However, in order to satisfy the requirements of a systematic treatise and to obtain a fixed starting-point for diagnostic purposes, it is necessary to outline the clinical characteristics of the disease.

By chlorosis we understand a disease with the following chief characteristics:

1. The disease occurs exclusively among females, is exceedingly common at puberty and throughout the succeeding decennium, and shows an inclination to recur.

[While all authorities agree that chlorosis is a disease of the female sex—to the practical exclusion of males—the assertion of von Noorden that the disease does not occur among males is unwarranted. Many competent authors might be cited to prove the occasional occurrence in young men. Any theory of causation that is based upon the exclusive occurrence of the disease in girls or women is open to question; at least its universality of application can be denied. Further reference will be made to the question of sex when the theories of chlorosis are discussed.—ED.]

2. The cardinal symptom of the disease is anemia or, more accurately, an impoverishment of the hemoglobin and red corpuscles of the blood. This anemia is reponsible for most of the other symptoms of the disease.

3. The disease apparently develops spontaneously—at all events all the causes which lead to similar extreme anemias are wanting.

4. If complications are absent, the disease impairs only the state

of nutrition of the blood without causing any deterioration of the nutritive process in general.

In reference to what is known of the nature of the disease we might add:

5. The anemia of chlorosis is dependent upon an insufficiency of blood production and not upon an increased destruction of hemoglobin and blood-corpuscles.

This definition needs certain explanations; further demonstration is also required to indicate in which direction the definition is to be extended:

1. Anemic conditions also occur in males, which are similar to the chlorosis of the female in their external phenomena and in the behavior of the blood. The sexes cause such a great variation in the clinical picture of the disease, however, that the differences are more striking than the points of similarity. The other blood diseases, such as the secondary anemias, pernicious anemia, and leukemia are always the same in both sexes. This is not so in chlorosis; the sex gives to the disease its distinctive characteristics. Until the actual nature of chlorosis has been more accurately established we can not lose sight of this long-recognized fact without being led into the most dangerous diagnostic errors. We may ultimately discover that chlorosis is due to definite anatomic changes in important organs, to anomalies of function, or to toxic effects, for example, the absence or excess of certain so-called internal secretions, and may then describe many apparently different affections under the heading of chlorosis. Until we have gained such a broad foundation, the chlorosis of the female should not be classified with the anemia of the male.

2. Chlorosis and anemia are not identical. The former is a disease, the latter is a symptom of a disease—in this instance, a symptom of chlorosis. In practice it is frequently difficult to diagnosticate or to exclude chlorosis where anemia certainly exists. The difficulties are greatest at that age of life in which chlorosis is most common, since every cause of anemia, whether it be external or internal, may at this time produce a disease, which differentiates itself from chlorosis by its course and consequences, but which nevertheless tends to present the features of a true chlorosis.

3. When we say that the development of the disease is apparently spontaneous, it must not be understood that external or so-called determining causes are always absent. We know very well, for example, that chlorosis or chlorotic conditions, at least, may be initiated by very different deleterious influences. It is, however, very questionable

whether these detrimental influences do more than cultivate the basis for the development of the disease. The general impression is obtained that chlorosis is a so-called "endogenous" disease—*i. e.*, a disease requiring a particular predisposition for its development. If the predisposition is marked the chlorosis occurs under all conditions; if the predisposition is weak, the disease breaks out only from the coöperation of some deleterious external influence.

4. In the course of the description of the disease it will be shown that chlorosis *per se* exerts no detrimental influence upon the nutritive process in general; although many patients become much reduced in the course of the affection, an explanation is always to be found in some complication or in the greatest neglect of the requisite measures.

5. From an analysis of the symptoms it will be shown that true chlorosis offers no indication whatever that it is an "anemia from blood destruction." The evidence is, nevertheless, still scanty and the author hesitates to include the sentence "the anemia of chlorosis is dependent upon an insufficiency of blood production" as an absolutely essential part of the definition. He is indeed convinced that time will demonstrate the truth of this assertion. He considers the anemia of chlorosis to be due to a pathologic impairment of the energy of the blood-forming organs.

If this conception proves correct we shall be able to define the disease with more accuracy. It would then be necessary to separate chlorosis from other anemias which are also due to deficient blood production and in which, likewise, there is no increased blood destruction. This may be done in one of two ways:

It is probable that we shall gradually become acquainted with all the causes which lead to relaxation of the blood-building organs in chlorotic individuals, and chlorosis will then be defined as a form of atony of the hematopoietic organs due to definite and specific causes.

On the other hand, the conception of chlorosis may be made to include all anemias which are not caused by increased blood destruction, but by deficient blood production. The disease which we now know as chlorosis would then represent only a variety of these anemias, and the peculiarities of the affection would be attributed only to the age and sex of the patient. An example for comparison is furnished by scrofula, which is separated from other clinical forms of tuberculosis by its external manifestations only.

ETIOLOGY AND PATHOGENESIS.

It has already been stated that we are not familiar with all of the causes which favor the development of the disease. From a practical standpoint, however, it is important to study the conditions under which chlorosis tends to appear and to present the theories which have been formulated concerning the disease. Most theories based upon reliable observations and clear trains of thought have a permanent value since they excite renewed investigation.

In reference to the etiology we follow the precedent of Immermann,[1] Hayem, and others, and differentiate between predisposing and exciting causes.

PREDISPOSING CAUSES.

Sex.—There is nothing to be added to the statements made in the previous section. We speak of chlorosis in regard to the female sex alone, and believe that the nature of the disease must be better recognized and defined before we may speak of chlorosis in the male.

The views of some noted authors[2] may be quoted upon this question. Immermann is extremely skeptical as to the occurrence of chlorosis among men, and knows of but 1 case in his practice which could be interpreted as such. The statements of Eichhorst, Niemeyer, Jürgensen, Hayem, Luzet, and Liebermeister are no less positive. Some authors, as F. A. Hoffman, and Sée, say nothing whatever about chlorosis in the male. Statistics of 181 cases of chlorosis in the Leipsic Medical Clinic have recently been published in which the disease affected the male sex eight times, a number that is unusually high as compared with all other reports (Ossent[3]). The clinical histories of these cases and confirmatory evidence as to the correctness of the diagnoses are unfortunately not given. The author can recall no case in which he would have been able to diagnose chlorosis in a male.

Age.—The most favorable age is the period from the fourteenth to the twentieth year. The first appearance of the disease nearly always occurs at this time; it begins much more rarely in the first half of the third decennium, and the initial onset at a later period is very unusual.

Niemeyer's warning against diagnosing and treating an anemia arising after the twenty-fourth year as chlorosis, without the most substantial evidence, still meets with the approval of cautious physicians. Isolated cases which admit of no other interpretation do, however, occur ("chlorose tardive," Hayem,[4] Rieder[5]). The chlorosis of mature years is much more frequent in females who were chlorotic in their youth, the chlorosis having either remained, or more or less lengthy periods having intervened between the individual attacks.

The following statistics show the period in which the disease first appeared:

Hayem[6] designates seventeen and a half years as the average age at which the disease commenced in 52 cases.

Harris[7] states that of 114 chlorotic patients—

63 were between 15 and 20 years of age;
41 " " 20 " 30 " " "
and 10 " over 30.

These statistics of Harris do not mention the time of the first appearance of the affection.

Ossent[3] says that of 150 patients, the chlorosis made its first appearance in—

22 before the 14th year;
84 between the 14th and 19th years;
29 " " 20th " 23d "
and 5 " " 24th " 33d "

R. Stockman[8] records 63 cases. The twenty-third year was the latest in which the chlorosis began. At the time of observation—

44 patients were between 13 and 20 years of age;
10 " " " 21 " 24 " " "
and 9 were beyond the 24th year of life.

The author's own statistics[1] with the results yielded are given on the succeeding page.

[1] These records, together with those quoted in the following sections, are partly taken from our notes and the clinical records of the Municipal Hospital, of Frankfurt a. M. The greater portion of the material, however, has been obtained from the case-books of the Second Medical Clinic of Berlin and of the Medical Clinic of Giessen. At this place we wish to thank my honored preceptors, Profs. Gerhardt and Riegel, for the use of the material in question. Altogether we have had the opportunity of consulting the clinical histories of about 260 cases. It will readily be understood that the entire series could not be utilized for every individual question, since the clinical notes, as well as the anamnesis, present condition, and course of the disease were not recorded in a uniform manner and did not always take every symptom into consideration.

Of 242 patients, the following were the ages at which the chlorosis made its first appearance:

2	younger than	12	years	of	age,
2	were	12	"	"	"
2	"	13	"	"	"
19	"	14	"	"	"
31	"	15	"	"	"
44	"	16	"	"	"
32	"	17	"	"	"
31	"	18	"	"	"
17	"	19	"	"	"
23	"	20	"	"	"
14	"	21	"	"	"
10	"	22	"	"	"
12	"	23	"	"	"
1	"	24	"	"	"
2	older than	24	"	"	"

Of these 242 patients, 149 had already had one or more attacks of chlorosis. Of these a recurrence took place in—

4	at	the	age	of	15	years,
10	"	"	"	"	16	"
13	"	"	"	"	17	"
16	"	"	"	"	18	"
13	"	"	"	"	19	"
21	"	"	"	"	20	"
21	"	"	"	"	21	"
14	"	"	"	"	22	"
15	"	"	"	"	23	"
11	"	"	"	"	24	"
6	"	"	"	"	25	"
4	"	"	"	"	26–30	"
1	"	"	"	"	30–35	"

Heredity and Predisposition.—Chlorosis frequently breaks out in young girls without the agency of any recognizable external influence, or the pernicious agencies which are held responsible for the disease bear no relation whatever to its severity. The latter statement is true only in the smaller number of cases. From experience with the origin of other forms of anemia, it may be said that the anemia of chlorosis is fairly well based upon external conditions and that its intensity is proportional to the intensity of the deleterious influence.

The disease arises often enough, although the conditions and habits of life are such that they directly seem to oppose the occurrence of anemia.

Such a quantitative disproportion between cause and effect is also encountered in the infectious diseases, but these are out of the question as far as chlorosis is concerned. It is also met with in diseases which are caused, or at least favored by, a predisposition. To this class belong gout, obesity, most cases of diabetes, arthritis deformans, myxedema, Basedow's disease, and many nervous affections. We are forced to suppose that in chlorosis there is also a predisposition that must prepare the soil before the external agencies are able to bring the disease to light.

Corresponding to this view we find that chlorosis frequently presents itself as a family disease. Very many patients state that their mothers have also been chlorotic, but it is rare to obtain accurate information upon the subject. It has been frequently observed, however, that all the female members of one and the same generation become more or less chlorotic at the age of puberty. Any experienced family practitioner will know of numerous such instances. In looking over old hospital case-books the author was unable to collect any data upon this point, since the anamneses were almost always incomplete in this respect. In the course of the last two years, however, he has made observations in 20 chlorotic individuals who had sisters over fifteen years of age.

In 4 instances none of the sisters was chlorotic; in 7 instances some of the sisters were chlorotic, some were not (yet?) chlorotic; in 9 instances all of the sisters had been chlorotic.

This small table refers only to patients in well-to-do families, in which everything possible had been done to maintain the health of the daughters.

It is repeatedly stated that chlorosis is particularly prone to occur when the parents have had syphilis, tuberculosis, gout, diabetes, or severe nervous diseases. We have seen no statistics to prove the truth of these statements.

[French writers particularly have insisted upon the frequent association of chlorosis and a tuberculous family history. Trousseau, Hayem, Jolly, and Byram Bramwell, among others, have established series of cases to prove this view. It must be remembered that chloro-anemia, difficult to distinguish from true chlorosis, is frequent in the incipient stages of pulmonary tuberculosis and may have had some influence in the supposed relationship referred to.—ED.]

The records of 217 cases at the writer's disposal contain definite statements concerning the family histories. Of these, 44 cases or 20.3 per

cent. had parents, brothers, or sisters affected with tuberculosis. The percentage is, if anything, rather small. In 17 instances the patients themselves certainly had tubercular antecedents (glandular or articular). Cases in which the tuberculosis did not seem to have completely disappeared were not utilized in these statistics.

The nature of the predisposition to chlorosis seems to be clear. It can be nothing else than a weakness in the hematopoietic system. It is very unlikely that corresponding macroscopic or microscopic changes will be found in the bone-marrow ; at all events we can not count upon them when conditions of functional weakness are present. We may follow Virchow[1] and Immermann, and call the condition "plastic adynamia of the blood-building organs." Virchow went further, as is well known, and believed that he had found the gross anatomic cause of this weakness of the hematopoietic organs in a congenital hypoplasia of the vascular system. In considering the subject from an anatomic standpoint and in neglecting clinical experience, Virchow has gone much too far. No one could ever admit that chlorosis is dependent upon such a permanent and incurable anomaly as arterial hypoplasia (for other evidence against Virchow's theory, see p. 386). Those writers who would trace chlorosis to a deficient development—*i. e.*, to gross anatomic hypoplasias and aplasias of the genitalia—will always meet with new difficulties. For every case which might be so interpreted there will be ten or twenty others in which there is no question of any gross anatomic deficiency in the essential parts of the sexual apparatus.

It corresponds much better with the facts to consider these three things—hypoplasia of the vascular system, retarded development of the genitalia, and plastic adynamia of the hematopoietic organs—as coördinated developmental disturbances, which may be found singly or in combination with each other or with various other "signs of degeneration." In showing the relation of chlorosis to retarded development of the genitalia, H. Stieda[9] has sharply emphasized this coördinated relation in a large number of cases. The want of dependence of chlorosis upon congenital narrowing of the aorta is still more marked. It may frequently happen that individuals with congenital hypoplasia of the vascular system may also have the milder developmental disturbance of the genitalia, which is evidently much more frequent and which leads to chlorosis; the pathologic anatomist who sees the patient succumb as a result of the vascular hypoplasia would consequently readily acquire the impression that the two anomalies were inseparable. It is forgotten that in the great majority of clinical cases the chlorosis arises

and disappears independently of anomalies of the vascular system; there may be small unimportant retardations of development ("degenerative signs") of the vascular apparatus, but surely no anomalies which are of importance for the entire circulation and for the nourishment of the tissues.

Of the three groups of congenital anomalies in question the "plastic adynamia of the hematopoietic organs" is evidently the mildest, since it may be completely overcome in most instances. The results of this anomaly become temporarily manifest in the majority of cases at that period of life in which the body is rapidly completing its development, when considerable strength is demanded, when the conditions of life and nutrition are frequently not so favorable nor proportionate to the new situation as they were in childhood, and particularly when the female organism is for the first time subjected to certain processes which are undoubtedly related to blood-formation.

The latter point is one of extraordinary importance. No theory which ignores the relationship between chlorosis and the establishment of sexual maturity can demand earnest consideration. The combined weight of facts is always directed to this particular point in question.

How shall we explain this connection? A superficial method of observation considers only the loss of menstrual blood. There has been no lack of authorities who designated the losses of blood as the immediate cause of the chlorotic anemia. This doctrine dates back to Trousseau,[10] with his "menorrhagic form" of chlorosis, and has recently found another champion in Dunin.[11] The accuracy of the idea becomes rather doubtful in view of the fact that most chlorotic patients have unusually scanty menses; they may be absent for months and yet a rapid recovery does not take place, while after other losses of blood of the amount of the catamenial flow a rapid regeneration may be observed which is complete in a few days. The connecting link between the functions of the sexual apparatus and the bone-marrow is by no means so apparent. The nervous system has been suspected and the disease interpreted as a reflex neurosis. Our knowledge of the so-called reflex neuroses and their influence upon metabolism is, however, not so intimate that we may call upon them without definite proof to explain such a sharply outlined clinical picture as is presented by chlorosis. To our mind, it is more probable that the newer studies upon the reciprocal chemic relations of the individual organs will throw more light upon the subject than any of the preceding hypotheses.

In addition to the congenital weakness of the blood-building apparatus which is usually overcome, but which in other instances may

never disappear, a cause for chlorosis might also be sought in an acquired weakness of the hematopoietic organs. This acquired weakness is to be found in some process going on in the sexual apparatus, since this form of chlorosis occurs only at the time of puberty.

To repeat briefly what has been said, we seek the cause of chlorosis in a functional weakness of the hematopoietic organs, which is partly congenital and partly acquired. Based upon this functional weakness, there occurs a temporary, or more rarely a permanent, true insufficiency of these organs—*i. e.*, chlorotic anemia. Disturbances of the relations existing between the female sexual apparatus and the blood-building process are necessary for the development of the disease.

An insufficiency of blood-formation developing without any relation to the genital apparatus would not be classified as chlorosis from our theoretic standpoint. External deleterious influences nevertheless play an auxiliary rôle, since they may increase the already existing weakness of the blood-building organs or in other cases actually produce it. It is of great practical importance to be familiar with these determining causes.

DETERMINING CAUSES.

We must not overestimate the range of so-called determining causes in chlorosis. Experience warns us that in the majority of cases there is no pernicious external influence worthy of note; in other instances their coöperation is not to be denied.

Unfavorable Nutritive Conditions.—If the total absorption of food is too small in youth, or if the nutrition is sufficient in general but wanting in certain respects, in the quantity of albumin, for example, the body is backward in development and blood-formation always suffers. In later years also, a deterioration of the quality of the blood, with or without a simultaneous loss of weight, is always one of the earliest results of bad nourishment. Similar conditions often obtain in young girls and help to bring about the attack of chlorosis. In the first place we must think of the many young girls who go to work immediately after they leave school. The working body demands a considerable increase in the amount of food, but the demand is not always complied with; the wages of young working girls are usually much too small to procure a nutritive diet, and, what is of especial importance in these years of life, a diet rich in albumin. Even when the wages are sufficient, the young girls are in total ignorance of the nutritive value of foods, and select a diet which is very satisfying, but which contains only a minimum quantity of actual nutriment. The position of young servant girls is not much

better. Families who take their servants directly from the school desk are usually in close circumstances themselves. They nourish themselves badly, and frequently can not be made to understand that scanty food is more harmful to the young person in their service than poor wages and unkind words. The contrast between the old and new conditions is still more marked when girls from the country hire themselves out in the city. The result of all these conditions is a retardation of further physical development, anemia, loss of flesh, or, at least, an absence of that filling-out of the body, which is to be expected in these years. Chlorosis often associates itself with this condition of affairs. It can frequently be established in hospitals that the disease is something more than a mere disturbance of nutrition. It is an everyday experience that young girls coming from places where the nutritive conditions are bad rapidly increase in weight—ten to twenty pounds a month is by no means rare. The chlorosis, however, does not get better, and recovery is delayed for a considerable time after a condition of good general nutrition has been obtained. It must not be thought, however, that young girls are insufficiently nourished in bad social conditions only. Even in the families of well-to-do citizens it frequently results from childish whims, from faulty inspection of the diet, and from an injudicious selection of foods and arrangement of meal hours. It does seem, however, as though this state of affairs is becoming more uncommon than formerly, and that proper attention is now paid to the sensible and sufficient nourishment of young girls in these classes of the population. If the nutrition is deficient, in spite of all this, there is usually some digestive disturbance present, such as gastric ulcer, nervous dyspepsia, constipation, and, by no means the least, the bad effects which ensue from wearing tight-fitting corsets. We very frequently meet with chlorotic young girls who are in an admirable condition of general nutrition, and who show the falsity of the idea that chlorosis must always be preceded by insufficient food, lack of digestive power, and deficient absorption. [Stockman insists that a deficiency of iron in the food is the exciting cause of chlorosis, while others assert there is deficient absorption of food of all kinds.—ED.]

Home Conditions.—In addition to the question of diet, the living and sleeping rooms deserve our first attention. Among the young girls of the lower classes it will be found that, with few exceptions, these conditions are the most unfavorable that could be imagined. There is always a deficiency of fresh air by day and by night in the sleeping and working rooms. The same unhygienic conditions are not infrequently met with in the houses of the rich; provisions are made

for all the conveniences and comforts, but air and light are both neglected. It is remarkable what close, dingy, musty sleeping rooms the physician often enters, although the reception rooms lack no luxury. It must be admitted, however, that these conditions have considerably improved in Germany in the last few years. Insufficient amounts of light and fresh air are certainly powerful factors in the development of anemic conditions; they consequently increase the predisposition to chlorosis and accelerate its appearance. They are, however, only several of many deleterious influences and they play quite different rôles in individual cases. The disease frequently appears in spite of the most favorable conditions of the home, and *vice versâ* an insufficient amount of light and fresh air is followed by true chlorosis in a very small percentage of cases. [Home-sickness seems to have some influence in the development of chlorosis. The editor has repeatedly commented upon the frequent occurrence of chlorosis among maids who have recently come to this country from Ireland, France, and other foreign countries. Some investigation has led him to believe that the conditions of life, the food, etc., are in nowise responsible, while nostalgia was so marked a feature in some of these cases that its importance was regarded as certain.—ED.]

Injudicious Bodily Exercise.—The influence of physical exercise upon blood-formation is not sufficiently established. General experience teaches that both too little and too much are detrimental, and have a particularly unfavorable influence upon the quality of the blood. In chlorosis, it seems to me that overexertion is of more importance than insufficient exercise. This is surely the case with many servant girls and with the majority of females of the working classes. In the latter instance, we must also remember that the physical exertion is usually in but one direction, that the girls work in unhygienic surroundings, and that the other conditions of life are likewise unfavorable. Altogether it amounts to overexertion of a body as yet immature, and we must consequently expect an unfavorable reaction upon the entire organism in general and upon the blood-making organs in particular. In other individuals of this class (in seamstresses, for example), and likewise in the upper circles of society, the amount of physical exercise is far below that required by health. In the latter class, however, this is not so bad as formerly, since an interest in the sports has rapidly become universal. This also has its dangers, since overexertion is common. Riding, tennis-playing, and especially the bicycle have conjured up or aggravated many a case of chlorosis where it had been hoped that these exercises would ward off the affection.

Clothing.—It has long been assumed that the tight clothing of the female has an unfavorable influence upon the general health, and chlorosis has also been made dependent upon this factor. Great stress has been laid upon this point recently, and many writers go so far as to give the corset the most prominent place among the etiologic factors of chlorosis. O. Rosenbach[1] and Meinert[12] are particularly pronounced in their advocacy of this view, the former dwelling upon the interference with the respiratory movements and the latter emphasizing the displacement of the upper abdominal organs, and the traction upon the nerve plexuses. Although we are not an advocate of the corset, and do not deny that injudicious lacing may cause actual disturbances of the functions of the stomach, intestines, and respiratory apparatus, and consequently that they can aggravate the chlorosis, we regard the standpoint of Rosenbach and Meinert as altogether one-sided. This point will be fully considered in a later section.

Sexual Influences.—At this place we will not speak of the very intimate relation which, according to our supposition, exists between the sexual apparatus and blood-regeneration. This will be found in the section upon Theories of Chlorosis. We may likewise disregard the relation of menstruation to chlorosis. It has previously been emphasized that menstruation *per se* can not be made responsible for the affection. The disturbances of menstruation are more probably the results, or the independent concomitants, than the cause of the disease. The anomalies of menstruation will be more appropriately considered under the head of Symptomatology.

There are still other influences acting through the genitalia which have been suspected of being the cause of chlorosis. Among these we would particularly mention the awakening of the sexual impulse without gratification of the same, and unnatural sexual excitement from rubbing the genitalia. The older literature upon chlorosis is rich in such references. In recent years much less stress has been laid upon this point, and this is rightly so. The idea that chlorosis is introduced or accompanied by a tormenting sexual impulse is certainly fallacious. Women who were chlorotic as young girls give credible evidence that the coöperation of this factor is to be denied. Women who have a recurrence of their chlorosis during married life complain rather of the extinction of the sexual impulse during the chlorotic attack than of the contrary. Lovesickness is also said sometimes to play a rôle in the etiology of chlorosis. General experience speaks decidedly for this view, but the manner of its influence upon the state of the blood is so obscure that it is still incapable of being understood and scientifically demonstrated.

THEORIES OF CHLOROSIS.

ONLY a brief statement of the most important theories of the pathogenesis of chlorosis will be given. The correctness of these theories can be but briefly discussed. Many facts for and against the individual hypotheses will be found in the section upon Symptomatology.

Virchow[1]: Chlorosis has as an anatomic basis of congenital origin a deficient development of the vascular system.

Virchow leaves the question undecided as to whether these conditions may be looked upon as constant. In his dissertation he does not state whether he regards the hypoplasia, which he found in the dead-room, as the cause of the deficient blood-formation, or whether he considers the hypoplasia of the vascular system and the hypoplasia of the blood as coördinated factors. Certain expressions seem to indicate that he inclines to the former view.

[" More recent studies (Paltauf, Ortner, Fraentzel) indicate that the congenitally small heart and aorta are more closely associated with the *constitutio lymphatica* and with cardiac disease than with chlorosis. This hypoplasia has been found in subjects never suffering from chlorosis, and the majority of chlorotics give no other evidence of such vascular anomalies and make complete and permanent recovery" (Ewing). It is not improbable, however, that in some cases this congenital vascular anomaly is an expression of a systemic condition that may predispose to chlorosis when other causes, such as the establishment of menstruation, are operative.—ED.]

Immermann[1]: Chlorosis is always dependent upon a deficient formation of blood (" plastic adynamia and functional anergia of the cytogenic apparatus "). The weakness of the hematopoietic organs may be partly congenital, and is then associated with aplasia of the vascular system, which Immermann designates as a higher grade of the " chlorotic anomalies of formation." The weakness may be acquired and manifest itself only temporarily. The disease breaks out at the age of puberty, because at this time special demands are made upon blood-production.

Beneke[13]: The development of the female sexual organs produces

certain reflex disturbances of the organs of digestion. These disturbances are the cause of insufficient absorption, of insufficient digestion, and of the loss of too much iron. It thus happens that, in spite of the nourishment being sufficient for ordinary needs, a lack of iron gradually develops, and this, combined with increased destruction of the red blood-corpuscles, leads to a decrease of the amount of hemoglobin in the blood; in short, to chlorosis.

Zander[14]: Chlorosis arises if the absorption of iron suffers. The digestive disturbances, especially the lack of hydrochloric acid, are due to the faulty absorption.

Bunge[1]: During pregnancy the maternal organism furnishes the fetus with a considerable amount of iron. It is not likely that the entire amount of this iron is absorbed and digested during the pregnancy of the mother. Bunge assumes that this iron has been previously stored up in the maternal organism. The female is prepared long in advance for the future conception and pregnancy. Bunge believes that this provisional storage of iron in the organs (liver, spleen) occurs at the time of puberty; when associatod with other deleterious influences it leads to a lack of hemoglobin in the blood. In support of this theory it might be mentioned that, according to L. Jones,[15] the blood of even the healthiest girls shows a decreased amount of hemoglobin at the time of puberty. On the other hand, Lapique[16] states (contrary to the analyses of the organs of animals by Bunge and Winternitz[17]) that the liver and spleen of the mature fetus contain less iron than is the case in individuals who have completed their growth.

Bouchard and Couturier[18]: Chlorosis is frequently, but not always, caused by a preceding dilation of the stomach which causes disturbances of nutrition, abnormal fermentations, and the production and absorption of deleterious substances.

Clark,[19] Duclos,[20] and, to a certain extent, Nothnagel,[21] believe that the main cause of chlorosis is to be found in constipation, which is responsible for abnormal putrefactive changes of the albumins. These poisons are absorbed, partly retarding blood-formation and partly promoting blood-destruction.

Forchheimer[22]: The hemoglobin is formed in the mucous membrane of the intestinal canal; chlorosis must be produced when this process is disturbed. Forchheimer suspects that this process is disturbed, because he found a poisonous albuminous substance, apparently an albumose, in the urine of chlorotic patients. He believes that this albuminous substance originates in the intestinal wall, and that it is formed from materials which are necessary to the formation of hemo-

globin. For some cause the synthesis of hemoglobin and hematin does not take place, and this results in chlorosis.

Meinert[1]: The anatomic cause upon which chlorosis depends is the gastroptosis produced by the corset. This results, first of all, in an increased irritability of the distorted plexuses of the abdominal sympathetic. If certain exciting causes supervene, the nervous system, prepared by the gastroptosis and its sequelæ, causes the chlorosis to appear. It is, of course, believed that nervous influences are responsible for the anemia. Briefly stated, Meinert says that chlorosis is a neurosis, and that in this instance the basis for the latter is furnished by gastroptosis. [E. Grawitz[1] does not accept the view of Meinert regarding the relation of gastroptosis to chlorosis. The frequency of gastroptosis in young girls is, of course, acknowledged, and the conditions in chlorosis are such as to increase this tendency. There is, however, no other connection between the two conditions.—Ed.] L. Jones[15] and Reinert,[24] although following another train of thought, likewise come to the conclusion that chlorosis is a neurosis, or that the chlorotic anemia is produced by nervous influences.

Murri[25]: Anomalies of distribution and velocity of the blood hold a prominent position among the conditions leading to chlorosis. They are caused by abnormal irritations of the vasomotors, and these abnormal impulses are received reflexly from the genital apparatus. This pathologic function of the vasomotors causes the blood, especially in the periphery of the body, to pass into the veins with a changed velocity, and consequently with a changed chemic composition. These slight variations in the velocity of the blood are further said to excite an increased destruction of the red elements, since it is known how sensitive these corpuscles are to an abnormal composition of the surrounding fluid. These deleterious influences are said to be particularly likely to occur in the winter months, thus explaining the considerable increase in the number of cases of chlorosis occurring at this time. In Germany we are certainly unable to confirm the latter observation.

v. Hösslin[26]: Chlorosis arises from the frequent loss of small quantities of blood, which occurs in the mucous membrane of the digestive tract, and which usually escapes observation. R. Stockman[27] and Dunin[11] likewise lay stress upon losses of blood, but more particularly upon those occurring during menstruation.

Clement[28] classifies chlorosis with the infectious diseases, since it is not infrequently accompanied by enlargement of the spleen.

[1] *Deutsch. Klin.*, No. 3, 1903.

Charrin[29] regards chlorosis as an auto-intoxication which arises from abnormal processes in the ovaries (menstrual auto-intoxication).

[Referring to the etiology of chlorosis, Grawitz[1] calls attention to the fact that hypoplasia of the heart and arteries may occur in men, but chlorosis is exceedingly rare. This point was recognized and emphasized by Virchow himself. There are, however, undoubted cases of chlorosis in young men. Wunderlich remarked that the disease occurs especially in young men of indifferent physique and who engage in occupations of a more or less sedentary character, such as tailors, clerks, etc. Grawitz does not accept the theory of an internal secretion as an important etiologic factor in chlorosis. He refers this view to the same category as to that which formerly ascribed hysteria to a similar cause. Considering the peculiar symptoms of the disease and the character of the blood, he suggests that the nervous system plays an important rôle in the etiology, and the peculiarities of the blood are referred especially to some anomaly in the formation of lymph rather than to any abnormal hemogenesis. There seems to be some alteration in the capacity of the blood-vessel to regulate the osmosis of liquid, and thus an accumulation of liquid takes place in the channels without a corresponding exudation.

In conclusion Grawitz[1] states, "I regard chlorosis as a neurosis which affects young persons at the age of puberty, girls and women as a rule, though not exclusively. It is favored by certain predispositions. The anemic condition of the blood is one of the accompanying symptoms of the neurosis, and is directly referable to the underlying nervous affection."—ED.]

v. Noorden (supported by Immermann[1]): I believe that chlorosis is founded upon a functional weakness of the hematopoietic organs, which may be either congenital or acquired. I am not of the opinion, however, that every anemia dependent upon defective function of these organs, should be designated as chlorosis, but wish to reserve the name chlorosis for disturbances of blood-formation which proceed from the sexual organs, and particularly for those which become manifest during the developmental period. It is evident from our present state of knowledge that we can not say what real connection exists between chlorosis and the sexual organs. With the proviso that my ideas are but a hypothesis, I will state what I believe to be the probable chain of events. In the female organism, which gives off considerable amounts of blood through the sexual organs every four weeks, there is normally a mechanism to replace rapidly and completely the amount

[1] *Deutsch. Klin.*, No. 3, 1903.

of blood lost. The stimuli which cause blood-formation proceed from the sexual organs (ovaries?) themselves, not through the reflex paths, but by means of the production of chemic substances which gain access to the blood and to the blood-building sites, and have the property of stimulating the hematopoietic organs. The hematopoietic organs are not dependent upon these stimuli coming from the sexual organs alone, but their loss, nevertheless, endangers the normal process of blood-formation, particularly in young individuals. If these stimuli are absent or weakened, chlorosis develops—*i. e.*, there is an insufficiency of blood-formation, which is caused by specific processes in the genital apparatus. If the hematopoietic organs are congenitally deficient, or if they are subsequently weakened by unfavorable influences, the disease would naturally be more likely to develop.

Nothing whatever can be said of the reciprocal chemic relations existing between the sexual apparatus and the hematopoietic organs; we can only assume that they are not indissolubly connected with the menstrual process, for the menses of chlorotic patients are by no means characteristic.

Even a few years ago such a theory as has just been stated could not have been suggested; now, when we know something of the importance of the so-called "internal secretions" and suspect the great rôle which they play in the organism, the justification of a hypothesis which makes chlorosis dependent upon an absence or weakening of an "internal secretion" can not be denied.

[Levy,[1] in a discussion on the nature of chlorosis, groups the theories under two heads: (1) The anatomico-clinical, which places the inception of the disease in the blood, the digestive canal, or the nervous system; and (2) that which regards the disease as an auto-intoxication. He regards it as certain that some forms of chlorosis occur in the period of puberty as a result of auto-intoxication, and, in particular, as a consequence of deficiency of certain secretions.—ED.]

[1] *Gaz. Des. Hôp.*, No. 88, 1903.

GENERAL SYMPTOMATOLOGY.

It has been mentioned that in rare cases pathologic conditions develop in children, elderly women, or males which strongly resemble chlorosis in their course and external phenomena; the description of the symptomatology, however, can only be based upon the chlorosis of young girls and women, which so often appears during the developmental period and in the first decennium after maturity is attained.

The patient first complains of tiring easily upon physical exertion, of an unusual shortness of breath in climbing stairs, and of a tendency to palpitation. The symptoms appear gradually and are at first scarcely observed; it is not until a careful examination is made that one discovers they have existed a long time. The mild disturbances tend to be most noticeable in the morning hours, while in the afternoon and evening the young women are not lacking in vivacity or capacity for exertion. After the prodromal symptoms have existed in varying degrees for some days or weeks, an increasing paleness of the skin and mucous membranes becomes apparent. This first becomes noticeable in the conjunctival and oral mucous membranes, the color not disappearing from the cheeks until some time has passed. In this respect there are marked individual differences. The quality of the blood is considerably impaired in most cases of chlorosis before the paleness of the skin becomes noticeable to the patient and her friends; it even happens that young women in the first stages of the disease are admired for their rosy complexions. This is explained by the fact that the vasomotors are very irritable and that the facial capillaries undergo a marked dilation under the influence of fresh air or psychic excitement. The appearance is, however, deceptive, since in the absence of such irritation the paleness of the complexion becomes all the more pronounced. In this early stage of the disease it is consequently of particular importance to pay more attention to the color of the mucous membranes than to that of the skin, for they are much less under the influence of psychic stimuli. In other patients the paleness of the mucous membranes and of the complexion go hand-in-hand from the beginning. We can, however, easily convince ourselves that the degree of paleness is by no means dependent upon the intensity of the changes in the blood alone.

Although a certain parallel is not to be denied, there are still other factors, particularly the original pigmentation of the skin, which also have a determining influence. Skins poor in pigment (blondes) as well as those rich in pigment (marked brunettes) favor the early appearance of the paleness, in spite of a proportionately small amount of blood degeneration, while a moderate amount of pigment seems to obscure the pallor for a considerable length of time.

By the time the previously described symptoms (lassitude, dyspnea, palpitation, temporary or permanent pallor) have fairly developed, most chlorotic cases become subject to menstrual disturbances, and these are more likely to occur if the individual is young and if the menses have been only recently established. An opportunity will be subsequently offered to study more accurately these disturbances of menstruation in chlorosis. For the present it suffices to say that the nature of these disturbances is subject to considerable variation. A very small percentage of cases have no anomalies of menstruation whatever throughout the entire course of the disease; in somewhat more than half of the cases the menses are completely absent, delayed, or of but a few days' or hours' duration, and the fluid may be clear and scarcely tinged with blood. Less frequently the amount of blood is too great and the periods are too frequent. Pain is not unusual before the flow is established and during the first day. The exactness with which the regular occurrence and duration of the periods is observed causes any menstrual variations to be noted, and this well-known symptom of the disease frequently arouses the suspicion of the patient or her relatives and directs attention to the previously neglected concomitant phenomena.

If the disease does not disappear spontaneously, as is frequently the case in the initial stage, or does not recover under appropriate therapeutic measures, the early symptoms increase in severity and new ones make their appearance. The capacity for muscular exertion becomes less; after short walks and particularly after climbing there is a marked sense of weariness in the limbs; physical exertion, walking, and housework consequently become distasteful. There is great lassitude and desire for rest after exertion. If the amount of muscular effort is considerable, air-hunger, a sensation of oppression about the chest and palpitation, do not fail to make their appearance. Most cases are affected in this manner; we might indeed say that no patient with pronounced chlorosis remains entirely free from these symptoms. If the actions of many chlorotic individuals are closely observed, however, it will be found that there are great variations both in the capacity for muscular exertion and also in the intensity of the subjective disturbances (fatigue,

disinclination, relaxation). This is true not only of different patients, but also of one and the same person at different times. These differences are entirely independent of the severity of the blood-changes and of the general physical development. In spite of a marked decrease in the amount of hemoglobin in the blood and of a rather delicate physique, girls and young women are frequently seen who suffer proportionately little with the disease, retain their energy, and accomplish an amount of work of which a healthy girl could be proud. Others, sometimes of robust physique, suffer early and to a marked degree; they can not be moved to make any ordinary exertion, and exhibit a high degree of relaxation and lack of energy. It frequently happens, as previously noted, that this relaxation of mind and body is most marked in the morning hours and disappears more or less in the afternoon and evening. This can go so far that young women who scarcely feel able to perform the lightest housework in the morning dance without difficulty for hours in the evening, and are admired for their sparkling vivacity. Between the cases with a retained capacity for exertion and those in which this capacity is impaired there are, of course, the most manifold gradations. In the severest cases all chlorotic girls and women are affected in practically the same manner in relation to their capacity for muscular exertion.

There are some symptoms which are usually associated and more common to the severer forms of the disease. They are headache, flickering before the eyes, blackness of vision which may last for seconds, minutes, and sometimes hours; flashes of color which occur when the lids are closed, ringing in the ears, a temporary indistinctness of hearing, dizziness, a feeling of emptiness in the head with the sensation of approaching insensibility, and actual attacks of unconsciousness. These phenomena almost never occur when the patient is in the recumbent position and only very rarely during walking, provided that this is not overdone. They much more frequently develop during long standing, which is badly borne by all chlorotics. It is by no means rare for chlorotic individuals to fall unconscious while standing behind the counter, about the stove, or in the streets during public celebrations. Carriage rides under a hot sun and long railway journeys have a similar effect. These fainting attacks naturally cause considerable alarm and bring the patient to the physician after the minor disturbances have been neglected for a long time.

The digestive apparatus is very frequently affected. The appetite is somewhat whimsical. Many chlorotics have no appetite whatever and lose flesh from want of nourishment. This most frequently occurs

where little attention is directed to the diet of the individual—in servants, for example, where the choice of food is limited. It is rather a case of aversion to the customary monotonous diet than of an actual loss of appetite. All sorts of annoying sensations are also complained of, which appear during the digestive period and cause the patient to fear eating a liberal meal. Among these are an indefinite sensation of pain and pressure in the gastric region, pains in the ribs, flatulence after eating, belching, and heartburn. Other patients complain more of slight dyspnea, palpitation, and of dizziness, which increases after eating. All these symptoms, however, do not belong to the regular concomitants of chlorosis. There are many patients in whom they are completely absent and who retain their appetite even in the more advanced stages of the disease. This corresponds with the clinical fact that chlorotic individuals, as a rule, do not lose flesh. This is often not the case, and the reason will be explained later. It nevertheless happens that peculiarities of appetite are rarely absent, even if the total amount of food ingested is sufficient. Very often there is a dislike for certain foods; this dislike is most frequently directed against meat, sometimes against all kinds of meat, sometimes against certain varieties, or certain methods of preparation. In other instances, certain appetites develop which must be designated as actual perversities of taste; for example, the desire for strong acids, the girls drinking vinegar or lemon-juice. In others, the opposite inclination becomes manifest, chalk, lime, and sodium bicarbonate being preferred. It still more frequently happens that the regular mealtime fails to excite the appetite, while in the intervals the desire for food is so strong that the patient becomes actually ravenous. In this respect, chlorosis resembles the early stages of pregnancy. The movements of the bowels are no more uniform or characteristic than are the caprices of the appetite. Sluggishness of the bowels is indeed frequently complained of, but we must not forget that this ailment is very frequent in young girls and women in general. If the constipation is not marked, or if other symptoms are absent, the physician hears nothing of it, and a standard is wanting by which to compare the frequency of constipation in chlorosis with its occurrence in healthy girls. We have studied this question for a long time in reference to the theories which claim that there is a causal relation between constipation and chlorosis, and can not agree with the statement that chlorotic individuals tend to present a much greater degree of constipation than their companions of the same age. When constipation does occur, it is due to a sluggishness of the ileum, as is the case in most other youthful individuals who complain of the same difficulty; it

is only after the lapse of considerable time and after great neglect that the large intestine itself also takes part in the slowing of the fecal movement.

Chlorosis has no immediate effect upon the mental power nor upon the psychic condition. This is evidenced by numerous cases in which the judgment and perceptive faculties remain intact throughout in spite of extreme anomalies of the blood, and where the sense of illness holds a direct and correct relation to the severity of the disease. On the other hand, chlorosis is, without doubt, particularly prone to awaken slumbering neuropathic and psychopathic tendencies. Since these tendencies, partly congenital and partly acquired, are quite frequently the dowry of growing girls and young women, it is no wonder that we so often encounter diseased manifestations of nervous energy, amounting at times to severe neuroses and psychoses. As a rule, these symptoms are very mild, insignificant, and only observed by the immediate friends of the patient. The patient is whimsical, easily influenced by trivial circumstances, and obstinate. This obstinacy is particularly common; the energy with which the personal wishes and inclinations are followed is frequently in marked contrast to the lack of energy shown in the performance of small daily duties and the carrying out of medical suggestions. This lack of energy, partly of pure psychic origin and partly the immediate result of physical weakness and incapacity for exertion, gives rise to discontent and morbid doubts. The less the chlorotic individual exerts herself the greater is the sentimental disturbance, and this may be manifested in various directions which are dependent upon the character and surroundings of the individual. These patients indulge in fits of religious enthusiam, in innocent love-dreams and the like, as the case may be. It was formerly incorrectly supposed that these fits of fanaticism, flightiness, and love-sick longings were natural attributes of chlorosis and intimately connected with the disease. In reality they are but feebly related to the affection. Chlorosis usually attacks young girls at a time when many are unemployed or half-employed, suspecting little and knowing nothing of the earnestness of life, when their knowledge is only superficial and when their unawakened or half-awakened senses so readily furnish them with a world of dreams, thoughts, and sensations. The greater the imagination and the more commonplace the external form of the social and home life, the more pronounced are these psychic effects. The chlorosis lessens the capacity for work and the consciousness of strength, thus producing a half-sick condition, necessitating indulgence, and favoring the psychic development in the direction indicated. Unless the indi-

vidual has such an inherited predisposition or external conditions favor such disturbances, these psychic symptoms are not to be expected. It consequently happens that we meet these sensitive, fanatic, love-sick chlorotics almost without exception in the classes that have found no sufficient employment to occupy the time of their growing daughters. Where great duties present themselves and where there is work to do; for example, among servants, peasants, factory girls, nurses, teachers, and young wives with heavy household cares, the chlorosis produces entirely different types. We find young women with that quiet tenacity and great self-sacrifice, which are peculiar to their sex, struggling against fatigue and weakness and in spite of their sufferings fulfilling their duty to the utmost until they collapse. There are also spoiled and overindulged chlorotic individuals who dream their way through life as long as nothing is required of them, and yet who frequently show how little chlorosis has to do with their state of mind when some great duty, such as the nursing of a patient or the care of children, suddenly presents itself.

In addition to fatigue, palpitation, and dyspnea upon exertion, the patients frequently complain of headaches. These headaches vary greatly and present little that is characteristic. There may be successive attacks of true migraine which afflict the patients for hours and days and then cease for a time. In other cases the pain is darting, localized to the temples, behind the eyes, or in the occipital region, coming and going at intervals throughout the day, appearing upon exertion—particularly when this is in the form of standing—and disappearing with rest, after a light luncheon or a few swallows of wine. Other patients complain of a dull, persistent pain, which is not sharply localized and which torments them throughout their waking hours. This last form, fortunately rare, is particularly disagreeable because it is very resistant to treatment and usually does not disappear until the chlorosis has been completely cured. The headaches tend to grow worse at the time of menstruation or at the time when the menses should appear but fail to do so. Few chlorotic individuals completely escape them, but the rôle which they play in the symptomatology of the disease is subject to the greatest variations.

Correspondingly frequent are the complaints of cold hands and feet and of a general sensation of chilliness throughout the body. These phenomena are naturally dependent upon the sluggishness of the peripheral circulation. In chlorosis the vasomotor mechanism is very easily excited. The contraction of the small peripheral arteries follows the irritation of cold more suddenly and permanently than in health, but the narrowing of the blood-vessels may also occur to a marked

degree from internal stimuli alone. An example is furnished by the "doigt mort," which is by no means uncommon in chlorosis. Upon the other hand, the excitability of the vasomotors also gives rise to symptoms of vascular dilation. This is manifested by an increasing sensation of heat, warmth about the head and burning cheeks which present a marked contrast to the general paleness of the skin. The conditions of vascular dilation are, however, much more fugacious and, on the whole, rarer than the symptoms of vascular constriction. The most frequent complaint is of cold feet. This phenomenon is sometimes almost permanent, or it occurs whenever the patients sit or stand in a cool room without sufficiently warm clothing about their lower extremities. In most cases this chilling of the feet occurs only at bedtime. As soon as the stockings are pulled off in a room that has not been heated, the sensation of cold begins in the feet and legs and may become so intense that it is absolutely painful; the skin is very pale and as cold as ice to the touch. In spite of friction and warm bedclothes this coldness persists for a long time and then gradually disappears.

While these varied subjective disturbances are developing, the objective examination of the patient will also reveal manifold changes. At this place these will be but briefly considered, since their detailed description will be found in the section upon special symptomatology. The most striking sign and the one which directs attention to the diagnosis is usually the paleness of the skin. This frequently shades off into a greenish tinge, which gives the disease its name in English and most other languages. This paleness is to be observed in the conjunctiva and in the visible mucous membranes of the mouth, nose, pharynx, and genitalia. The blood obtained from puncturing the skin is clear, more or less transparent, and flows more readily and profusely than is the case in other anemias. By microscopic examination the red blood-corpuscles seem strikingly clear and unevenly colored ("chlorosis of the red blood-corpuscles").

The pulse rate is increased, but if it is studied for some time and the patient gets over the first excitement which follows every medical examination, the heart beats more slowly and practically approaches the normal rate. The area of cardiac dulness is usually enlarged, more toward the right than toward the left. Blowing systolic murmurs are heard over one or more of the valves; venous murmurs are likewise present in the great vessels of the neck and, in more severe cases, also in the femoral veins.

The examination of the lungs reveals a somewhat more rapid and

superficial breathing than normal. The lower borders of the lung are frequently somewhat high up in spite of a well-maintained capacity for expansion. The vesicular breathing is sharp and clear.

Scarcely any pathologic condition can be ordinarily found in the abdomen; sometimes certain areas are sensitive to pressure and the stomach or intestines may be more or less distended with air. Certain authors emphasize the frequent occurrence of a low position of the stomach or even of gastric dilation. The area of splenic dulness is often enlarged; the spleen is, however, much more rarely accessible to palpation.

The demonstrable objective changes in the sexual organs are the previously mentioned anomalies of menstruation, leukorrhea, sensitiveness in the ovarian regions (Ovarie), and not infrequently some variety of retarded development. It might also be mentioned that the external genitals of many very youthful cases of chlorosis are better developed than their age would indicate. Other diseases of the sexual organs occur in chlorotic as well as in healthy girls, but they are accidental coincidences and have no connection with the chlorosis.

The urinary excretion is abundant. The urine is pale and has a low specific gravity. It is only in the severest cases that the urine is scanty and concentrated. Even in the severest and most chronic cases of uncomplicated chlorosis, the urine rarely contains more than the normal traces of albumin, which we are practically unable to demonstrate at the bedside with the ordinary reagents. Sugar is never present. The other urinary constituents will be fully considered at an appropriate place.

The feces, as a rule, are of the ordinary color and consistence; in severe cases the movements may contain so little coloring-matter that they are grayish yellow and resemble the clay-colored stools of jaundiced individuals.

The general nutrition is usually good, as has previously been mentioned, but it is not correct to consider this as characteristic of chlorosis, since there are entirely too many exceptions. To make a statement corresponding more accurately to the facts of the case, we would say that the general nutrition of the chlorotic individual remains satisfactory if the diet is good, varied, and appetizing, and that a decrease in the body-weight is more a result of neglect than of the actual disease.

Of the long list of symptoms peculiar to chlorosis, a certain number are always absent in the individual case. No two cases are absolutely alike. In this individual the nervous symptoms, such as loss of energy, capriciousness, headache, dizziness and a tendency to fainting are more

marked; in that one, dyspnea, fatigue upon slight exertion, and palpitation are observed; in other instances the gastric and intestinal disturbances, the vasomotor stimulations and paralyses, and the menstrual anomalies are the chief features of the disease. The manner in which the affection manifests itself is dependent upon the character and disposition of the patient, upon external conditions, and whether this or that organ has lost its power of resistance from heredity or previous disease. We have always found an intense pleasure in studying the previous history of every case as minutely as possible, thereby trying to find an explanation for these individual peculiarities.

The general course of the disease is as variable as are the individual symptoms. The chlorosis may begin suddenly, like an acute disease, and even attain its acme within a few days. This seldom occurs, however, but is most frequent in young girls who have been attacked by the disease soon after the first menstruation. These are always severe cases, which progress with marked nervous symptoms (headache, dizziness, disturbances of vision) and with great weakness, so that a suspicion of a severe cerebral disease is aroused. The prognosis is nevertheless relatively favorable, since the disturbances also tend to a rapid disappearance. The cases of subacute (in two or three weeks) or chronic development are more numerous. When these cases are left to themselves they drag along and do not recover for many weeks or months. It is, however, only the mildest attacks, which cause scarcely any disturbances worth mentioning, that receive no treatment whatever. As soon as more marked symptoms present themselves almost every chlorotic girl is given some preparation of iron, either with or without medical advice. If this treatment is systematically carried out, and if other scarcely less important measures are not neglected, considerable improvement or even a cure is obtained in some weeks, but a longer time must be counted upon for the average duration of the disease. This is because the necessary energy is rarely employed in the treatment and because the tendency of the chlorosis to recur becomes manifest. The individual case is indeed so much benefited in from three to six weeks that marked symptoms are no longer present, yet, before the composition of the blood has completely returned to the normal, and before the paleness of the patient has disappeared, fresh exacerbations of the disease are observed. It consequently happens that while many patients are permanently cured in a few weeks or have no recurrence for a year or so, the disease persists in varying degrees of intensity in an equally large number of cases for months and even for years. Chronic chlorosis, although not dangerous to life, is nevertheless a lurking disease which

rarely fails to cast its shadow upon the later life of the individual. For the development of individual organs, for the production of a body and mind capable of resistance, and for the storing of energy for the battle of life, it is of the greatest importance that the individual should enjoy perfect health and a sensation of physical and mental strength just at the age when chlorosis so frequently makes its appearance. Those who are weakly for a long time during these years, only too easily remain physical and mental cripples throughout their entire existence.

SPECIAL SYMPTOMATOLOGY.

THE BLOOD.

When Immermann wrote the chapter upon the blood-changes found in chlorosis for von Ziemssen's great *Handbuch der speciellen Pathologie and Therapie*, in 1879, he could dismiss the subject with a few words, and was in reality forced to confine himself to the published reports of the amount of hemoglobin and of the number of red blood-corpuscles in chlorotic blood. Since that time an enormous amount of energy has been directed to the examination of the blood in general and of chlorotic blood in particular. The advances of knowledge, unfortunately, do not always correspond to the labor employed, and we must admit that the examinations of the blood have not yet thrown enough light upon the most important and decisive questions in relation to the pathogenesis of chlorosis. Those who work with these questions and wish to lay claim to thoroughness must examine the blood in every possible respect by the most varied methods and in a manner not yet dreamed of. The different methods do not always give a unanimous result and it is not always possible to consider the different findings from a common standpoint.

A description of the methods employed for the examination of the blood in chlorosis may be omitted in this article. These may be found in special works. The recent and beautiful books of E. Grawitz[3] and of R. v. Limbeck[31] are worthy of particular mention. They both contain complete descriptions of the refined methods in modern use.

THE RED BLOOD-CORPUSCLES AND THE HEMOGLOBIN.

The first trustworthy accounts of the quality of the red blood-cells in chlorosis were furnished by J. Duncan. In 2 (female) patients[1] he found a normal number of red blood-corpuscles in blood poor in coloring-matter. From this the followers of Duncan, rather than he himself, drew the conclusion that the characteristic blood-change in chlorosis consists of a diminished amount of hemoglobin in the individual red

[1] The third case certainly was not chlorosis. The patient was a young man with enlargement of the spleen.

blood-corpuscles, while the number of these bodies is not decreased. This small observation of Duncan caused a great number of blood-examinations to be made. In looking over the text-books of to-day, the general impression, without doubt, is that Duncan's theory is right—at least in the sense that in chlorosis the diminution of the amount of hemoglobin is more pronounced than the decreased number of blood, discs. Since the author's first studies on the composition of the blood (1879), he has directed earnest attention to this question at the bedside. Although unable to furnish statistic proof from the large number of individual examinations, made for the most part in the clinics of Riegel and Gerhardt, the general result may be stated as follows:

a. In chlorosis the number of the red blood-corpuscles and the percentage of hemoglobin are simultaneously decreased.

[In Thayer's series of 63 cases (Osler, *American Text-book of Medicine*, vol. ii., p. 199) the average number of red corpuscles was 4,096,544; in Cabot's series of 192 cases (*Clinical Examinations of the Blood*) the average was 4,052,000; and in Da Costa's series (*Clinical Hematology*) the average in 106 cases was 3,876,000. These figures represent the editor's experience and correspond to the results of all recent writers.—Ed.]

b. As a rule, the hemoglobin percentage is much more markedly decreased than would correspond to the diminution in the number of red blood-corpuscles. As a result there is a decreased amount of hemoglobin in the individual corpuscle.

[The average percentage of hemoglobin was 42.3 per cent. in Thayer's series; 40.4 per cent. in Cabot's cases; and 41.3 per cent. in Da Costa's.—Ed.]

c. This relation between the hemoglobin and the number of red blood-corpuscles just described (under *b*) is maintained in all grades of chlorosis, and likewise throughout the different stages of the disease. It is most striking, however, in the first attacks of a severe form in very young girls, much less noticeable in the recurrences, in the chronic forms, and in the chlorosis of older persons. It is also more pronounced in patients who retain a good condition of general nutrition than in girls who are badly nourished and considerably underweight.

In reviewing the literature for the decision of this question we are confronted by many difficulties. This is preëminently due to the fact that authors have not always diagnosed their cases with the same degree of precision. Our present conception of chlorosis is of a purely clinical character, and we can not always feel confident that the author has excluded cases of anemia which were dependent upon germinating pul-

monary tuberculosis, upon gastric and intestinal diseases, and upon conditions of malnutrition. A diagnosis of chlorosis can not be made simply from the fact that there is a relatively marked decrease of hemoglobin. Although the statement that in chlorosis the hemoglobin is more markedly diminished than the number of red blood-corpuscles may be true, the assumption that a preponderance of the hemoglobin decrease over the decrease in number of red blood-cells makes a diagnosis of chlorosis, is undoubtedly false. Otto,[34] for example, in his admirable experiments upon the effect of venesection upon the composition of the blood, found that in the regeneration of this fluid the corpuscular elements increased much more rapidly than did the amount of hemoglobin. The same fact is shown in the clinical histories reported by Laache[35] and other writers. In certain stages between a venesection and complete regeneration, the blood consequently has a composition which, according to Duncan, is characteristic of chlorosis.

There are likewise cases of markedly emaciated individuals (for example, in carcinoma, in sepsis of long duration, and in syphilis) in which the percentage of hemoglobin is much more diminished than the number of red blood-corpuscles. Following Laache's example, in such cases we speak of a decrease in the "value of the red blood-corpuscle."

A brief review of the literature, with reference to the larger and more profound studies alone, may give a proper conception of the conditions found in chlorosis.

Leichtenstern[36] determined the "coefficient of extinction" of the blood by means of Vierordt's spectral apparatus. While the blood of healthy women had an average coefficient of extinction (E) = 1.237, in chlorotic girls he found the following values for E: 0.757, 1.014, 1.111, 1.017, 1.060, 1.105, 0.880, 1.031, 0.957, 1.060, 0.960. The greatest difference between the normal and pathologic values amounted to 40 per cent. (Case 1). Blood-counts are wanting; but Leichtenstern's monograph contains a comprehensive opinion of the qualities of the red blood-corpuscles which must carry great weight, from the rich experience of the author. He considers it a settled fact that in many cases of chlorosis the oligochromemia has its only basis in the decrease in the number of red blood-corpuscles (oligocythemia), the individual blood-discs being of normal size and containing the normal amount of hemoglobin. In other cases the descriptions of Andral, Hayem, and Sörensen are to the point; they claim that the blood-corpuscles of chlorotic individuals are poorer in hemoglobin and also partly smaller than normal.

Hayem,[37] in the first edition of his book, approached rather closely to the theory of Duncan. In one-third of his 22 cases he found the number of red blood-corpuscles over four million, while the coloring-matter of the blood was decreased to one-half. In the other cases the number of blood-corpuscles was also considerably decreased, but the diminution in the amount of hemoglobin was still much more apparent. The highest hemoglobin value found by Hayem was 71 per cent. of the normal amount; the average value was 52 per cent.

Laache[35] arrived at other conclusions in his valuable and exhaustive monograph. He described milder cases of chlorosis in which the clinical phenomena of the disease were so distinctly marked that the diagnosis could not be doubted, yet the blood showed scarcely any deviations from the normal worth mentioning (either in respect to the number of red blood-corpuscles or to the amount of hemoglobin). In other cases (13) the blood-corpuscles and the hemoglobin were considerably diminished, sometimes approximately to the same extent; as a rule, however, the coloring-matter usually suffered much more. He found as a minimum value for the number of red blood-corpuscles 2,440,000, as an average value 3,185,000. The maximum decrease of the amount of hemoglobin contained in the individual corpuscle ("value of the red blood-corpuscle") was to 50 per cent., the average decrease was to 66 per cent. Laache's monograph contains no proofs for the assertion of Duncan and Gräber (see below): that in chlorosis, in spite of a normal or almost normal number of red blood-corpuscles, the amount of hemoglobin may sink one-half or even more. Laache's observations upon blood-regeneration in chlorosis are of great interest. He saw the coloring-matter increase much more rapidly than the number of red blood-corpuscles. Laache's measurements of the size of the blood-corpuscles are also important. Malassez[38] had stated that the corpuscles in chlorotic blood are enlarged. Laache found the average normal diameter to be 8.5 μ, the maximum 9 μ, and the minimum 6.5 μ; his average values in chlorosis did not deviate from these figures. No enlargements are recorded; in 2 instances the red blood-corpuscles were smaller than normal (4.4 μ and 4.5 μ). The lack of uniformity in the size of the individual elements is, however, particularly emphasized.

Of all recent authors, E. Gräber[39] comes closest to the old theory of Duncan. The results of Gräber are more important than those of Duncan, since they are more numerous and obtained by far more accurate methods. Gräber goes so far as to state that a normal number of red blood-corpuscles with a lessened amount of hemoglobin is thor-

oughly characteristic of chlorosis and an important diagnostic proof of the presence of the disease. Among 28 cases he records:

7	cases	with more than	5	millions	of	blood-corpuscles,	
13	"	"	4–5	"	"	"	"
8	"	"	3.8–4	"	"	"	"

In contrast to 12 to 13 per cent. (of the total blood), which is the normal amount of hemoglobin in the blood (determined by Hüffner's spectrophotometer, the best method up to the present time), he found the hemoglobin amount in his 28 chlorotics, as follows:

in 4	cases	higher than	7	per cent.,
" 4	"	between	6 and 7	"
" 5	"	"	5 " 6	"
" 9	"	"	4 " 5	"
" 6	"	"	3 " 4	"

A decrease of at most a fifth in the red blood-corpuscles consequently corresponds with a sinking of the hemoglobin of three-fifths or even of two-thirds. In reference to the size of the corpuscles, Gräber records 7.5 μ as the average (in contrast with 7.8 μ as the normal diameter). This average value was found in nearly every individual case; in accord with the results of Laache, however, the difference between the maximum and minimum diameters was greater than in normal blood. For example, the same blood frequently contained corpuscles with diameters of 6 μ and of 10 μ. Gräber emphatically denies that any actual diminution of the red blood-cells is a part of pure chlorosis. When, in addition to a poverty of hemoglobin ("chlorosis of the individual corpuscle"), there is added a decrease in the number of corpuscles, complications are always present—that is, there is a coöperation of other "causes productive of anemia," such as hematemeses, menorrhagias, or deficient nutrition. It can not be disputed that Gräber selected his cases of chlorosis with particular care and excluded all in which the diagnosis was in any way dubious. A sufficient explanation for the striking results of his examinations is nevertheless wanting; other authors, such as Laache, for example, arrived at directly opposite results and were no less careful in their selection of cases.

Oppenheimer[40] made a report of the quality of the blood in 32 cases of chlorosis; only 26 of these, however, are to be regarded as pure types of the disease. The number of blood-corpuscles varied between four and five million, usually averaging four and a half million, and consequently showing no decrease. The amount of hemoglobin, on the contrary, was almost always decreased more than 30 per cent., often 40 per cent. and more. Oppenheimer, on the whole, con-

sequently agrees with the statements of Duncan and Gräber. He particularly emphasizes the diagnostic value of such findings as these, since other pathologic conditions which cause a similar composition of the blood (convalescence from severe hemorrhage or disease) are not likely to be confounded with chlorosis. In secondary anemias of different origins Oppenheimer found, in accord with Gräber, and we might say with all other authors, a constant slight decrease in the number of corpuscles with a decreased amount of hemoglobin. He admits, citing illustrative cases, that the coöperation of complications disturbs the typical condition and that the number of red blood-corpuscles may be considerably diminished.

[Cabot[1] tabulates his cases as follows:

	Cases.
Between 7,000,000 and 8,000,000	1
" 6,000,000 " 7,000,000	2
" 5,000,000 " 6,000,000	26
" 4,000,000 " 5,000,000	72
" 3,000,000 " 4,000,000	64
" 2,000,000 " 3,000,000	26
" 1,000,000 " 2,000,000	1
Total	192.—Ed.]

Reinert[41] treats of 18 cases of pure chlorosis in an excellent monograph. In 5 instances the number of blood-corpuscles was over four millions, in 13 cases the number was less. Among these are a number of cases with only three million of blood-corpuscles or less. The coloring-matter of the blood was, almost without exception, decreased to a much more marked degree than the number of red blood-corpuscles. He consequently decides "that the disproportion between the number of red blood-corpuscles and the amount of hemoglobin at the expense of the latter is usually much more strongly pronounced in chlorosis than in ordinary anemia." The expression "chlorotic blood-corpuscles" (Hayem), which refers to a diminution of the coloring-matter and of size of the individual corpuscles, is in some measure consequently descriptive. Although the characteristics are not so well developed, this kind of a corpuscle is also found in the majority of anemias, and Reinert himself furnishes numerous examples.

v. Limbeck[42] reports the results of the blood-examinations in 16 cases of chlorosis in which frequent counts and estimations of hemoglobin were made. In v. Limbeck's patients the diminution of hemoglobin is almost without exception more marked than the decrease in the number of corpuscles; his figures are nevertheless directly contradictory to the results obtained by Gräber, Oppenheimer, and also to those of A. Maucher,[43] who published a small series of 9 cases. At the

[1] *Clinical Examination of the Blood.*

time when treatment was commenced, v. Limbeck found but once that the number of corpuscles was more than four million; they were five times between three and four million, five times between two and three million, and five times still less.

Eichhorst[44] has recently published a small collection of 35 cases, in which no uniformity can be perceived in the relation between the hemoglobin and the number of blood-corpuscles. In this series we find records of but 11 in which there were more than four million corpuscles; 11 were between three and four million, 9 between two and three million, and 4 less than two million. As a rule, the amount of hemoglobin was more markedly decreased than would correspond to the number of corpuscles; in the severest cases of anemia both were decreased in practically the same proportion.

R. Stockman,[8] who has rendered many services to the study of chlorosis in recent years, gives the following table of the results of the blood-examinations in 61 cases of pronounced chlorosis in girls and young women:

Number of cases.	Number of corpuscles.	Percentage of hemoglobin.	Average percentage of hemoglobin.
6	4½–5 million.	46–66	52.6
9	4–4½ "	30–60	44.8
11	3½–4 "	35–54	42.7
15	3–3½ "	22–44	33.2
10	2½–3 "	30–48	35.7
8	2–2½ "	20–46	31.6
2	1½–2 "	25–28	26.5

In this table four and a half million corpuscles and 80–90 per cent. of hemoglobin (Gower's hemoglobinometer scale) were regarded as normal.

R. Schmaltz[45] reports the following figures from 13 patients:

5 had	4–5	million corpuscles;	hemoglobin average	6.03 per cent.
5 "	3–4	" "	" "	5.14 "
3 "	2–3	" "	" "	5.40 "

In this table 12 per cent. of hemoglobin is regarded as normal.

The reports of Eichhorst, Stockman, and Schmaltz consequently agree that in chlorosis the hemoglobin alone may be diminished, but that, as a rule, the blood-corpuscles are likewise decreased.

We will forego mentioning other individual communications. A copious bibliography of the literature may be found in the works of Reinert[41] (p. 141) and v. Limbeck[31] (p. 302).

The work upon the subject, as may be seen, has not led to a uniform result. The followers of Duncan and Gräber claim that their opponents have not examined pure and uncomplicated cases of chlorosis—a

reproach that is undoubtedly too far-reaching in its generality. On the other hand, it becomes evident that prejudice has caused the followers of Duncan and Gräber to exclude cases which did not fit into their pattern, although they came within the "clinical" conception of chlorosis.

The question is of sufficient importance to demand further investigation. If we will find something new, we must give the most accurate attention to the correctness of the diagnosis of "chlorosis" and follow out the simultaneous coöperation of other influences productive of anemia, in the recognition and exclusion of which free scope is given to our discretion. It is also much more urgent now than formerly to determine whether the age and race of the patient, the stage and duration of the disease, the existence of previous chlorotic attacks, the occupation, the kind of diet, and the therapy employed, are not of decisive importance for the conditions found in the blood. According to the author's opinion, some of these individual factors are responsible for the many contradictory findings. Upon p. 368 will be found the results of his experience, formulated in short sentences.

There is but little to be said in reference to the morphologic peculiarities of the red blood-corpuscle.

So far as the size of the corpuscles is concerned, the original and much-cited assertion of Malassez[38] (derived, indeed, from the examination of a single case), that the diameter was abnormally large, has not been confirmed in its generality. From the careful measurements of Gräber and Laache and also from personal observations, it may be said that the results are subject to great variations. We frequently meet with no deviations from the normal; in severe forms of the disease, however, a simple glance through the microscope will discover striking differences in size between the corpuscles in the field of vision, which are more marked than one ever encounters in healthy blood. This is, however, not characteristic of chlorosis. The absolute measurements of Laache and Gräber have been previously recorded upon p. 371.

[Cabot, Grawitz, and others insist on the usual diminution in the average size of the red corpuscles.—Ed.]

If megalocytes and microcytes are observed in the blood of anemic individuals, blood-corpuscles with changed shapes (poikilocytes) are never wanting. Ordinarily, they are present only in small numbers in the blood of chlorotics; in the milder grades of the disease they are entirely absent. On the other hand, there are severe individual cases in which extraordinarily large numbers of poikilocytes are found. The authors have observed a patient affected with undoubted chlorosis whose

blood, in the beginning, showed more poikilocytes than regularly formed blood-corpuscles. After ten days' treatment with arsenic the poikilocytes had almost completely disappeared. R. Muir[46] mentions a similarly extreme degree of poikilocytosis in a case of chlorosis, and adds to his report a handsome illustration of a specimen of the blood. These cases are rare and exceptional; we must be familiar with them, however, since we could readily be led astray from the diagnosis of chlorosis by a surprising find of marked poikilocytosis.

[Smith[1] found an increase of the total volume of blood by the carbonic-oxid method. The average volume in 21 cases was 4883 c.cm., the normal being 3240 c.cm. In some cases the volume was nearly double the normal. As the specific gravity of the plasma is normal, there would seem to be an increase of normal plasma and an actual increase in the number of red corpuscles.—Ed.]

Nucleated red blood-discs hold about the same relations as do the poikilocytes. After their appearance in the circulating blood had long been looked upon as an extreme rarity, Ehrlich[47] was successful, with the aid of his staining method, in first demonstrating the presence of nucleated red blood-corpuscles in all cases of severe anemia. The first special mention of nucleated red blood-corpuscles in chlorosis is to be found in a dissertation by C. Jacoby[48]; the blood-preparations were prepared and examined by Ehrlich himself, and the cells were of the large nucleated variety known as megaloblasts. The same cell forms were found later by Hammerschlag[49] in a case of chlorosis. The small nucleated red blood-corpuscles (normoblasts) are much more frequent. With careful searching and the employment of a good staining technic they will always be found to some extent in every moderately severe case of chlorosis. From daily examinations of the blood, we have frequently been able to establish that their number varies considerably and apparently without any regularity. Sometimes every specimen contains one, two, or more nucleated corpuscles; on other days many specimens must be examined before a single one is found. That they suddenly appear in large numbers in a similar manner to the "blood-crises"[50] first described by the authors, as Neudörfer[51] mentions, the former has never seen in spite of diligent investigation, although we has seen this quite frequently in other forms of anemia. From the investigations of Neumann, Bizzozero, and particularly those of Ehrlich, no doubt can exist concerning the significance of the small nucleated blood-corpuscles (normoblasts). They are the evidence of active regenerative processes in the blood-forming organs (bone-marrow). Clinical

[1] *Jour. of Physiol.*, vol. xxv., p. 6.

facts, however, do not allow of the conclusion that their appearance in the blood is the forerunner of a speedy cure of the chlorosis. The increase of the nucleated cells, moreover, coincides just as frequently with deteriorations as with improvements in the hemoglobin percentage and general condition. It would seem from this that the regeneration in the blood-forming organs does not occur everywhere with the same degree of energy. While in one location it may be so active that young, immature nucleated structures are thrown out into the blood; in other situations the process may still be at a very low ebb. Ordinarily, the course of chlorosis is much too extended and the regeneration of the blood much too limited for the process of recovery to have a visible expression in the blood itself in the form of a sudden flooding of the blood with nucleated elements.

According to E. Maragliano and P. Castellino [52] blood-corpuscles are to be found in severe forms of chlorosis in which the agonic phenomena ("slow necrobiosis") described by them may be recognized.

THE COLORLESS ELEMENTS.

The statements in regard to the white blood-corpuscles are much fewer in number. The older authors speak only of "normal condition," of "slight increase," or of "slight decrease." Characteristic changes in number and form, as they occur in other diseases of the blood, were denied. In a general way this old teaching, based more upon estimate than upon actual count, still holds good. The newer investigations of the blood, directed especially toward the white corpuscle, have indeed furnished us with more accurate information concerning their number, the proportion in which the individual varieties are found, and the occasional appearance of the rarer forms, but nothing has been changed in the old statement that the leukocytes are not subject to any characteristic change in chlorosis.

The following may be mentioned as some of the results obtained by individual investigators:

In 7 cases of chlorosis, Sörensen [53] found the average ratio of white corpuscles to red to be as 1 : 616. In 28 cases Gräber found the ratio

twice greater than	1 : 300			
7 times between	1 : 400	and	1 : 500
3 " "	1 : 500	"	1 : 600
5 " "	1 : 600	"	1 : 700
3 " "	1 : 700	"	1 : 800
3 " "	1 : 800	"	1 : 900
3 " "	1 : 900	"	1 : 1000
2 " "	1 : 1000	"	1 : 1100

Gräber[55] regards the ratio as normal—and we agree with him—as long as it remains between the extremes of 1 : 400 and 1 : 1000. Since the red blood-discs were undiminished almost throughout Gräber's cases, his figures show that not only the relative, but also the absolute, number of white cells were almost always normal. Reinert[56] came to absolutely the same result in his examinations of the blood of 10 cases. With two exceptions the absolute numbers were between 4000 and 10,000 white corpuscles in the cubic millimeter; larger numbers were observed in 2 instances (11,000 and 13,000). The relative proportions usually remained between 1 : 400 and 1 : 900; temporarily the ratio in individual cases was somewhat less. In 11 cases of chlorosis Muir[57] counted between 2000 and 8000 white blood-corpuscles; the relative proportion always remained within the limits designated as normal by Gräber. According to R. Müller[58] the increase of the white corpuscles after the ingestion of food ("digestion leukocytosis") is much less in chlorotic than in healthy individuals.

The mass of white blood-corpuscles, as is well known, is composed of a number of very different forms. The study of these was first made possible by Ehrlich's[59] fundamental work. We are indebted to one of his pupils, Einhorn,[60] for the earliest communications concerning the relative proportions of the forms of leukocytes in chlorotic blood. In 4 cases he found 9.28, 11.46, 21.6, and 52 per cent. of lymphocytes, while the remainder of the white corpuscles were to be classified among the mononuclear and polymorphonuclear cells. For the proper valuation of these figures it is important to remember that the same author found the healthy blood to contain 20–30 per cent. of lymphocytes. The investigations of Gräber[61] were more extended; the percentage of the lymphocytes was mostly normal (according to Gräber, normal = 15–35 per cent., average 24.5 per cent.). In only 2 instances was the number of lymphocytes considerably increased above this amount, reaching 40 and 61 per cent. We will limit ourselves to the statement of these facts, because we do not yet sufficiently appreciate what significance is to be attributed to a slight increase or decrease of the lymphocytes.

A slight relative and absolute increase of leukocytes with coarse eosinophilic granulations has frequently been described by such investigators as Eichhorst.[62] The author's personal experience confirms the correctness of this observation in individual cases; the exact counts, however, are not at his disposal. Such counts are to be found in the articles by Canon,[63] H. F. Müller, and Rieder,[64] and Zappert.[65] The normal number of eosinophile cells usually varies between 50 and 250

in the cubic millimeter; they comprise about 1–4 per cent. of the white corpuscles. A greater number may, however, be exceptionally encountered in healthy individuals, reaching 11 per cent. (Zappert) and 20 per cent. (Rieder and Müller). Canon, who furnished the first statistics upon the eosinophiles in chlorosis, records 2 cases with 0.75 and 5 per cent. In Müller and Rieder's 7 cases of pure chlorosis the percentages lay between 1.14 and 3.6 per cent. in 6 instances; in 1 case 9.6 per cent. was observed. In 11 cases Zappert found the absolute number to vary between 97 and 500; the relative proportion was between 0.65 and 3.74 per cent., only once rising to 8.54 per cent. None of the authors named have attributed any diagnostic or prognostic significance to slight increase or decrease in the number of eosinophile cells. Only Neusser,[66] who attempts to draw far-reaching conclusions in various conditions of the blood, believes that a particular nosologic position and a better prognosis must be given to the chloroses with a marked increase of the eosinophile element.

It is to be mentioned as a rarity that Hammerschlag[67] found large mononuclear leukocytes with neutrophilic granulations (myelocytes) in the blood of very severe cases of chlorosis. The author has never seen such a cell in numerous well-stained specimens obtained from severe cases.

Muir[46] is the only author the writer has found who makes exact statements in regard to the blood-platelets. He regards from 200,000 to 300,000 platelets in a cubic millimeter as the normal number in healthy individuals; in chlorotic blood they were, almost without exception, considerably increased, the number in most cases being between 350,000 and 400,000. Hanot and Matthieu,[68] without making any accurate counts, had previously called attention to the increased number of platelets found in chlorotic blood and had utilized this fact in the explanation of the thromboses occurring in chlorosis.

CHEMISTRY AND PHYSICS OF THE BLOOD.

Specific Gravity and Dry Residue.—The decrease in the specific gravity and in the dry residue holds a relation to the diminution of the number of red blood-cells and hemoglobin. A complete parallelism between the hemoglobin percentage and the specific gravity could naturally be expected only when all the other constituents influencing the specific gravity of the blood, particularly the albumins of the serum, remain unchanged. On the whole, this is true of chlorotic blood, and A. Hammerschlag[68a] comes to the conclusion that "In chlorosis a constant relation exists between the hemoglobin percentage

and the specific gravity, since a definite hemoglobin percentage in different patients corresponds to the same specific gravity. It consequently follows that we may estimate the amount of hemoglobin from the specific gravity, and it is only necessary to obtain the specific gravity to judge of the condition of the disease." He then gives the following table, based upon the results obtained by himself and Schmaltz,[69] for the computation of the amount of hemoglobin from the specific gravity :

Specific gravity.	Hemoglobin.
1033–1035	25–30 per cent.
1035–1038	30–35 "
1038–1040	35–40 "
1040–1045	40–45 "
1045–1048	45–55 "
1048–1050	55–65 "
1050–1053	65–70 "
1053–1055	70–75 "
1055–1057	75–85 "
1057–1060	85–95 "

In this table 95–100 per cent. hemoglobin (methods of Fleischl or Gowers) is taken as the normal amount. When we reflect that the more convenient methods of determining the hemoglobin percentage at the bedside are combined with great sources of error, excluded only by long practice, and that the determination of the specific gravity (by the methods of Schmaltz, Hammerschlag, Lloyd Jones) may be carried out with great exactness, the suggestion of Hammerschlag becomes clearly practical and acceptable. Stintzing and Gumprecht[70] have indeed shown that, both in the investigations of Hammerschlag and also in the similar ones of Siegl,[71] Schmaltz, and Scholkoff,[72] the hemoglobin percentages do not always go exactly parallel with the specific gravities. From this would follow, according to the views of these authors, the uselessness of Hammerschlag's comparative table and the still more accurately computed one of Schmaltz.[73] We can not share in these objections, but we do think that the slight incongruities which are found between the specific gravity and hemoglobin percentage-curves may be explained by the uncertain methods of hemoglobin estimation. If we wish to make very accurate scientific investigations upon the percentage of hemoglobin of the blood we must always confine ourselves to direct estimations of hemoglobin ; we should then, however, employ only really good and exact methods and not choose instruments which give rise to all sorts of errors (v. Noorden [74]). For the purpose of obtaining information at the bedside, for judging the amount of the decrease in hemoglobin, and to determine the advance of the increase or decrease of the coloring-matter of the blood of the individual cases, the estimation of the specific gravity is, however, sufficiently accurate. The

tables[1] of Hammerschlag (see p. 379) or of Schmaltz are then to be employed, and we may rest assured that a direct estimation of the hemoglobin by one of the more convenient methods in vogue (Fleischl, Gowers, etc.) would not have furnished any more accurate results. This is only to be recommended for chlorosis, since it has been established in this disease that the dried residue of the serum, which also has an important influence upon the specific gravity, deviates very little or not at all from the normal (see p. 381). The amount of albumin in the serum suffers only in the very severe cases (E. Grawitz[30]), and the specific gravity of the entire blood would then naturally indicate a smaller percentage of hemoglobin than was actually present.

As has just been indicated, the dry residue of the entire blood may also be determined instead of the specific gravity. The serum albumin being approximately constant and a change in the amount of contained salts having such a trivial influence, a decrease in the dry residue is to be referred to a diminution of the percentage of hemoglobin. The procedure was first employed by the author for the express purpose of ascertaining the amount of hemoglobin; some of the results so obtained were published in the dissertation by Lipman-Wulf.[75] The method was more accurately studied and tested by Stintzing and Gumprecht.[70] With the exception of small differences, having scarcely any practical import, the results agree with those obtained by the estimation of the specific gravity. Stintzing and Gumprecht give the following comparative table for chlorosis (the so-called "relative" hemoglobin values have been transformed into percentages—normal = 12.5 per cent. in healthy women):

Dry residue.	Percentage of hemoglobin.
12.5 per cent.	3.75– 5.00
13.4 "	5.00– 6.25
15.8 "	6.25– 7.50
18.3 "	7.50– 8.75
18.8 "	8.75–10.00
19.0 "	10.00–10.60

These figures also are true only for chlorosis, in other anemias which cause a decrease in the serum albumin the dry residue is somewhat less with the same amount of hemoglobin. Stintzing and Gumprecht were able to confirm the previously known fact that during recovery from chlorosis the dry residue of the blood, or its hemoglobin, increases much more rapidly than the number of blood-corpuscles (see p. 370).

A few figures may elucidate the behavior of the specific gravity and of the dry residue of the blood in chlorosis.

[1] G. Diabella has recently worked out this question in a most thorough manner.—*Arch. f. klin. Med.*, Bd. 57, S. 302, 1896.

In healthy individuals the specific gravity of the blood varies between 1055 and 1060, the lower figures being more frequent in women. In chlorotic girls and women—

Hammerschlag[68]	found	1035–1045.5
Lloyd Jones[76]	"	1035–1049
Schmaltz[69]	"	1030–1049
Hammerschlag[77]	"	1036–1052
Menicanti[78]	"	1034–1046

According to Stintzing and Gumprecht, the dry residue of the blood in healthy women amounts to 18.4–21.5 per cent. In 13 cases of chlorosis, at the height of the disease, the same authors record in 8 instances values between 11.7 and 16 per cent., in 5 instances values between 16 and 19.4 per cent. The figures of E. Grawitz[79] vary between 13.8 and 16.2 per cent. The author's results in the years 1889–1892 were mostly obtained from very severe cases, and are as follows: in 7 instances 11–13 per cent., in 4 instances 13.1–16 per cent. In 11 observations made by Maxon[80] the dry residue varied between 11.4 and 17.5 per cent.

The concentration of the serum, which is not without significance for the critical judgment of the conditions just described, was specially studied by Becquerel and Rodier, and by Hammerschlag. The normal specific gravity varies between 1028 and 1032. Becquerel and Rodier[81] give 1028.1 as the average value in chlorosis; in 30 cases Hammerschlag[77] records nothing less than 1027 and nothing more than 1032. The numbers most frequently recurring are 1029 and 1030. The results obtained by Lloyd Jones[1] and E. Grawitz correspond throughout, but Grawitz[30] adds that in very severe cases of chlorosis the serum is also affected, losing some of its albumin and consequently exhibiting a lower specific gravity and less dry residue. He mentions 2 cases with 7.28 and 7.60 per cent. of dry residue respectively (in contrast with 10 per cent., which is about normal). The nutritive condition was evidently poor at the time, because when the diet became richer and the patient gained in weight the concentration of the serum rose rapidly to the normal long before the hemoglobin percentage had experienced a similar increase.

We are indebted to the investigations of v. Limbeck and F. Pick[82] for certain information in reference to the relative proportions of the **albuminous substances in the serum.** The first and second

[1] Lloyd Jones designates 1027.1 as the normal average value of the specific gravity of the blood in girls under fifteen years of age, 1028.1 in girls over fifteen. In chlorosis he found 1025.5–1029, with an average of 1027.3, a practically normal value.

cases showed 34.53 and 38.3 per cent. of globulin respectively; the large remaining percentage was albumin. These figures are to be found in the table which these authors published upon the composition of the normal serum; the normal table, indeed, more frequently shows a somewhat smaller percentage of globulin.

According to the analyses of Becquerel and Rodier[81] the amount of fibrin is increased in chlorotic blood; they record 3 per cent. of fibrin, while normal blood contains only 1.9–2.2 per cent. Neither of these observations have been of value as yet for the critical investigation of the chlorotic process.

Isotonic Value of Serum.—In concluding the consideration of the characteristics of the serum the results of a few experiments in reference to its isotonic value are to be mentioned. There are only two observations—those of v. Limbeck.[83] He found the isotonia of the blood-corpuscles (or of the plasma) to equal that of 0.38 and 0.4 per cent. solutions of sodium chlorid (the normal, according to v. Limbeck, is 0.44–0.48 per cent.).

Mineral Substances.—Of the mineral substances occurring in the blood, iron has naturally excited the most attention, since it is a constituent of the hemoglobin. The oldest and still the most important analyses were made by Becquerel and Rodier.[84] In contrast to the normal amount of 0.486–0.575 per cent., the bloods of six chlorotic individuals showed an average of only 0.319 per cent. of iron. Since that time the theory of the iron impoverishment of the blood in chlorosis has been generally accepted, and it is only very recently that this statement has met with contradiction. In 6 cases Biernacki[85] found the percentage of iron in the blood either not diminished at all, or not diminished to the degree that the decreased amount of hemoglobin would indicate. He finally concludes that the impoverishment of hemoglobin is by no means the real chemic characteristic of chlorotic blood, but that the substance of the corpuscles may even be abnormally rich in iron and hemoglobin. The pale color of the blood is caused by the decrease of other coloring-matters, and its lowered specific gravity is sufficiently explained by the decreased percentage of albumins. Although the dissertation of Biernacki gives the impression of careful work, we must look upon his results with some skepticism, since they contradict all previous experiences in the chemistry of the blood.

Of the other constituents of the ash of the blood, we are especially interested in chlorin (or sodium chlorid), potash, and phosphoric acid. Previous investigations are unfortunately not sufficient to furnish clear and complete information in reference to the quantitative variations of

these substances at the height of the chlorosis and during the course of the disease. There are many contradictions which can scarcely be solved with our present knowledge. We certainly must not put implicit confidence in every analysis of the ash of the blood, since such analyses are the most difficult in chemistry and but few physicians are competent to make them.

It may be supposed *a priori* that those salts occurring chiefly in the red cells will be found in diminished amounts in chlorosis, while those occurring chiefly in the serum will be found in normal or even relatively increased quantities. This conclusion is nevertheless not imperative, since the phosphates of the red corpuscles may increase or decrease completely, independently of their hemoglobin percentage. Without entering upon a discussion as to the range of the observations, we will state the previously obtained facts.

Becquerel and Bodier:[84]

	Total blood.		
	In health.		In chlorosis.
Sodium chlorid	0.35–4.00 per ct.	(average = 0.390 per ct.)	0.310 per ct.
Phosphates	0.25–0.65 "	(" = 0.354 ")	0.441 " (average).

Biernacki:[85]

	Total blood.	
	In health.	In chlorosis.
Sodium chlorid	0.441–0.468 per ct.	0.479, 0.437, 0.427, 0.474, 0.474, 0.532 per ct.
Potash	0.160–0.174 "	0.127, 0.128, 0.120, 0.104, 0.125, 0.061 "
Phosphoric acid	0.0729 "	0.056 per ct.

The individual numbers are arranged according to the degree of hemoglobin impoverishment. The first five values of sodium chlorid and potash and the isolated value for phosphoric acid were obtained from mild degrees of anemia (hemoglobin decreased to one-half or to one-third). In the sixth case the hemoglobin percentage was diminished to one-fourth of the normal value.

v. Moraczewski:[86]

	Total blood in chlorosis.
Chlorin	0.2605, 0.2910, 0.2340, 0.293 per cent.
Phosphorus	0.0466, 0.0753, 0.0816, 0.036 "

v. Moraczewski designates 0.1–0.2 per cent. of chlorin, and 0.1 per cent. of phosphorus as the normal percentages. In chlorotic blood, therefore, he found the phosphorus decreased and the chlorin increased.

The author's assistant, Dr. Pickardt, found the following conditions in a chlorotic:

Blood: Dry residue = 13.9 per cent.
Hemoglobin calculated from the dry residue = 5.8 per cent.
Hemoglobin by colorimetric determination = 5.6 per cent.
Chlorin = 0.324 per cent.
Blood-corpuscles = 3,800,000.

At the time of the withdrawal of the blood the urine contained 0.42 per cent. of chlorin. The amount of chlorin in the urine varied between 0.42 per cent. and 0.49 per cent.; upon a salty diet the daily amounts of chlorin in the urine were: 9.2 gm., 6.15 gm., 8.84 gm. The blood for examination was taken upon the last day.

Alkalinity.—Many investigations have been carried out in reference to the alkalinity of the blood. Reliable figures are wanting, however, since the ordinary methods for determining the alkalinity furnish rather inaccurate results. The first reports come from de Rezi,[87] who records a moderate diminution of alkalinity. The investigations of v. Jaksch[88] led to a similar result. These analyses were contradicted by those of Gräber,[89] who used the same methods as those employed by v. Jaksch and found an increased alkalinity. Peiper[90] and W. H. Rumpf[91] agree with Gräber. The position of Rumpf is to be particularly emphasized, since he designates the increased alkalinity as an essential quality, differentiating chlorosis from other forms of anemia. He says: "By the increased alkalinity of the blood, chlorosis proves itself to be a chemic disturbance of the plasma which progresses with alterations of form, size, and coloring-strength of the red blood-corpuscles." Drouin[92] reports 1 case with increased and 1 case with diminished alkalinity. Fr. Kraus[93] determined the quantity of CO_2 in venous blood (H. Meyer's method of determining the alkalinity). Since the quantities obtained were within normal limits (36.97 and 37.01 per cent. of CO_2 by volume), he objects to the teaching of Gräber. v. Limbeck and Steindler[94] likewise obtained normal alkalinities by other methods.

We will not enter into a discussion upon these contradictory results, since the important studies of A. Loewy[95] have impaired the value of these and similar determinations of alkalinity. Loewy was able to demonstrate the inadmissability of all methods that worked with opaque blood; he produced proof showing why they must furnish contradictory results. According to A. Loewy's experimental studies, there remain but two methods which may be employed:

1. The determination of the amount of carbonic acid in the blood (employed only by Fr. Kraus in chlorosis). It is true that we learn absolutely nothing about the total alkalinity of the blood or of the serum, but we do learn something about a portion of the blood which is physiologically effective in a definite direction, namely, the portion which is of importance for the interchange of gases.

2. Titration of laked blood. In addition to the alkali effective as a carbonic-acid carrier, this procedure also reveals a certain amount of

another alkali, the function and disposition of which are as yet unknown. The alkalinity of laked blood is much higher than that formerly obtained from opaque blood. In healthy persons Loewy found: 100 gm. of blood = 447–509 mg. of NaOH. Among the patients in the author's wards who were examined by A. Loewy,[96] at the request of the former, there was a girl with chlorosis. At the height of the disease the alkalinity was equal to 662.3 mg.; during improvement to 541.8 mg. NaOH for 100 gm. of blood. Other investigations, with the aid of the titration method of Loewy, the only one now admissible, have not yet been carried out.

REVIEW.

If we review the preceding discussion, the judgment pronounced at its beginning will not seem too severe. In the course of the last twenty years a great amount of earnest effort has been devoted to the investigation of the blood of chlorosis, and yet we have acquired scarcely any facts which are absolute or of practical significance. It is to be hoped that the suggestions furnished from the confused mass of loosely connected individual observations will be productive of systematic and well-planned investigations.

In closing the author will review the most important points. The following statements may now be made in reference to chlorotic blood:

The decrease of the hemoglobin percentage is constant. According to all authors it is more marked than the diminution in the number of corpuscles. Some go so far as to deny any decrease of the latter in pure cases of chlorosis. This is without doubt an exaggeration. It is not justifiable to exclude those frequent cases in which the clinical diagnosis has been accurately made and designate them as complicated because of a decrease in the number of corpuscles, since the blood described as typical by Duncan and Gräber is not to be held up as a standard. In the meantime the conditions which produce a decrease in the number of corpuscles as well as an impoverishment of the hemoglobin are not yet sufficiently established.

In all severe cases an irregular distribution of the coloring-matter and irregularities of form of the red corpuscles are constant; the appearance of normoblasts in large or small numbers is also constant—at least in severe cases. In these respects severe forms of chlorosis resemble all other forms of anemia.

The condition of the white blood-corpuscles is normal in all essential points. In this respect chlorotic blood differentiates itself from many other forms of anemia.

The dry residue and specific gravity of the blood decrease at ap-

proximately the same rate as the hemoglobin, which permits conclusions to be drawn from these factors in reference to the hemoglobin percentage. In pure cases of chlorosis the density of the serum is not decreased.

Of the mineral substances of the blood, iron suffers a diminution corresponding to the loss of hemoglobin. That which has been learned in reference to the other mineral substances is so insufficient and contradictory that a conclusion can not be drawn either as to their significance or as to the diagnosis of the chlorotic process.

THE VASCULAR SYSTEM.

In chlorosis the vascular apparatus is the most frequently affected of all the systems of organs. Some of these changes are the most regular concomitants of the disease.

HYPOPLASIA OF THE VASCULAR SYSTEM.

Some have gone so far as to bring chlorosis into a close etiologic relation with pathologic-anatomic changes in the vascular apparatus. After Rokitansky[97] first pointed out that a permanent and almost incurable chlorotic condition is found in women with hypoplasia of the vascular system and genitalia, R. Virchow[1] made a thorough study of this question. He published the reports of some autopsies in which the aorta was thinner and of smaller caliber, and in which there had been other developmental disturbances of the arterial system. Since the extensively quoted work of Virchow, we have not gained much additional information upon this point; it is to be particularly noted that no extensive report of such autopsies has since been published. Individual confirmatory results have, however, not been wanting. We mention the cases of Gilly,[98] Tissier,[99] and one of Köckel's.[100] In the autopsy reports, by Bollinger,[101] Rendu,[102] and a second case by Kockel, nothing is said about hypoplasia of the aorta.

Some have since gone beyond Virchow's own statements, and—purporting to have the authority of Virchow—have represented the condition of affairs as if chlorosis was always due to the congenital narrowness of the aorta and other vascular hypoplasias. The simple clinical reflection that the narrowing of the aorta is a permanent and incurable condition, while chlorosis is but a temporary and easily curable disease in the great majority of cases, should have prevented this error. Before we can accept the lessened caliber of the aorta and its branches as the anatomic cause of chlorosis, new and abundant material must be furnished by careful and coöperative work in the hospital and autopsy room. Among the cases of Virchow, as well as among those published

by other authors (Lewinski[103]), there are some which can not be classified as chlorosis without considerable hesitation. From previous clinical and anatomic material we simply know that a lessened caliber of the aorta and its branches, in both sexes—whether it be congenital or acquired in childhood—can produce a diseased condition in the maturing body which resembles chlorosis to a certain extent. As a rule, these individuals are backward in general physical growth, and particularly in the development of the osseous and muscular systems. Arrested development of the sexual organs is found more frequently in girls than in boys, a fact particularly emphasized by Rokitansky. Paleness and transparency of the skin, delayed menstruation, palpitation, and dyspnea upon physical exertion, and, not infrequently, heart murmurs, help to complete the resemblance to chlorosis. No less confusing is the circumstance that the actual symptoms of the patient first develop at puberty, or, at least, at a time when a greater amount of physical effort is demanded—consequently during the period of life in which chlorosis usually becomes manifest. These forms of anemia and of cardiac and muscular weakness are indeed incurable and persist throughout many years. Many die in their youth as the result of this or that pernicious influence upon their feeble constitutions, and then appear upon the post-mortem table as "chlorosis with a lessened caliber of the aorta and its branches," while others, escaping the dangers of complicating diseases and of overexertion of the heart, reach a mature old age in spite of the vascular anomaly. In reference to the fate of such individuals we would direct attention to the excellent descriptions of the results of vascular hypoplasia which were published by Fräntzel.[104]

At this place the author wishes to cite a brief description of an instructive case:

A young girl had been in perfect health until fifteen years of age, but even as a child she had been of slender frame, was always pale, and required more than ordinary attention. During her sixteenth year she became unconscious while playing tennis, since which time she has become paler and suffers frequently from palpitation. The menses had not as yet made their appearance. She was given a great deal of iron, later Roncegno water, and was sent to chalybeate baths in her seventeenth year. There was no improvement either in the paleness of the skin or in the tendency to palpitation and dyspnea. I was consulted by the family physician to decide which chalybeate bath was indicated for this obstinate case of chlorosis. Since the heart and lungs seemed normal, the urine always free from albumin, and no deleterious influences could be found either in the external conditions or in the habits of the patient, there had been no doubt as to the correctness of the diagnosis of "pure chlorosis." The girl was tall and thin, the subcutaneous fat was well developed, as might have been expected from the carefully selected diet of the patient; the musculature, on the contrary, was considerably below normal. The skin was very pale, transparent, and had a cyan-

otic tinge at the finger-tips; the nails were very thin and brittle. The breasts were poorly developed and consisted entirely of fatty tissue, no glandular substance being palpable; the nipples were not larger than those of a child ten years of age. The heart was enlarged to the left and presented a strong, heaving apex-beat; the dulness extended to the right as far as the middle of the sternum. In addition to clear tones, a systolic murmur could be heard all over the heart, being particularly loud over the pulmonic cartilage. With the head erect, no murmurs could be heard in the veins of the neck. The right radial pulse was of moderate size, the left was considerably smaller. Walking rapidly about the room caused the pulse-rate to increase from 80 to 96 beats. The young woman, although in her eighteenth year, had not yet menstruated. There was scarcely any indication of pubic hair; the external genitals resembled those of a child. It was plainly to be seen that we had to do with a case of retarded development, similar to those described by Rokitansky, and not with a case of true chlorosis. When the author examined the blood upon the following day, he found that it had a specific gravity of 1052 and contained 4,900,000 corpuscles to the cubic millimeter. In spite of the extremely anemic appearance of the patient, the blood did not correspond in the slightest degree to that of chlorosis. In reference to the further progress of the case, it may be stated that the girl gained some strength during a prolonged sojourn at the seacoast, but that after the lapse of two years and in spite of repeated courses of iron she has remained just as weakly and poorly developed as before.

If cases like the one just described are grouped with chlorosis, the theory of Virchow may still meet with further confirmation. From a clinical standpoint, however, we must regard such a course as inadmissible. If attention is directed to this point it will not be difficult to separate the cases of true chlorosis from those of retarded development.

If we admit that with a lessened caliber of the aorta and its branches diseased conditions may develop which resemble those of true chlorosis and by inaccurate examinations may be confused with it, and if we further state that individuals with vascular hypoplasia are as particularly predisposed to chlorosis as they are to other diseases, and if we finally recognize that congenital deficiencies of the hematopoietic organs are not rarely combined with congenital deficiencies of the vascular apparatus in the same individual, it seems to the author that the clinical teaching has gone as far as it dare to approach the one-sided teaching of the pathologic anatomist.

We will leave these pathologic-anatomic discussions and turn our attention to the pathologic changes in the circulatory organs which are observed during life.

THE HEART.

Palpitation.—Almost all chlorotics complain of palpitation, but the nature and the degree of the palpitation are very variable. There

is not always a perfect parallelism between the palpitation and the anemia.

The most frequent form of palpitation is that dependent upon physical exertion. It is not present during rest, but makes itself manifest as soon as rapid or prolonged muscular movements are carried out (in going up stairs, for example). This is regularly associated with accelerated and deeper breathing. If the pulse and heart are examined at this time the pulse-rate is found to be increased and the apex-beat is more powerful; it is, consequently, not a simple subjective palpitation, such as is so frequently complained of by neurasthenic and hypochondriacal patients in whom no corresponding physical signs can be elicited. The excited action of the heart does not disappear immediately after the completion of the muscular effort, but usually remains for several minutes or even for a quarter of an hour. During this time the size and frequency of the pulse vary beneath the palpating finger; true arythmia is very rare, and there are usually simply periods of increased and decreased frequency of the pulse-rate. During the palpitation the pulse-wave is large, irregular, and dicrotic; more rarely it is small. The form of palpitation just described is the only one which is to a certain extent proportionate to the degree of anemia, both in the individual case and by comparison in different patients. Although the palpitation is present, it is not always equally disagreeable to the patient. Some chlorotics pay no attention to it, and others put it foremost among their complaints; many feel the palpitation only when they have time for self-observation, almost forgetting it during psychic excitement and when the attention is diverted. It consequently often happens that a chlorotic girl can not climb a flight of stairs in the morning without the annoying sensation of palpitation, and yet she can dance for hours in the evening in spite of it and never give it a thought.

The acceleration and accentuation of the heart's action, as well as the increased rate of respiration, are natural results of the anemia. They are to be regarded as compensatory factors for the hemoglobin impoverishment of the blood. Blood which is poor in hemoglobin can not take up as much oxygen on its way through the lungs nor carry as much oxygen to the cells of the body. If the amount of oxygen required is momentarily increased by muscular exertion, accessory forces must be called into play to furnish the necessary quantity. These forces are found in the increased work on the part of the heart and lungs, and they work together so that the blood streams through the pulmonary capillaries more rapidly and more blood comes in contact with more air in the same space of time. These are consequently

useful factors which equalize the difficulties of obtaining oxygen that are due to the quality of the blood.

In addition to this compensatory palpitation, as it were, there is frequently a second form—nervous palpitation—which appears without being produced by physical exertion. It is by no means always present, but is characteristic of individual cases, mostly affecting nervous persons and those with neuropathic tendencies. This palpitation occurs usually in attacks which last from several minutes to a quarter of an hour and which increase the pulse-rate to double or more. In other instances it is of shorter duration, only a fraction of a minute, and then it occurs at more frequent intervals, accompanying the change of the thoughts or of the sensations. A severe palpitation will often be complained of, when an objective examination will reveal no actual acceleration or accentuation of the heart's action. Nervous palpitation may be accompanied by dyspnea, but this is never so pronounced as in the compensatory form, although the sensation of oppression and lack of air is sometimes quite decided.

The third form is permanent acceleration of the heart's action. We have encountered this symptom most frequently in very acute cases of chlorosis and in those in which the disease was quite severe. Whether we examine the patient erect or recumbent, awake or asleep, we always find a high pulse-rate—100–110 and over. The pulse-wave is large and abrupt. In these cases we are frequently able to establish the coexistence of other symptoms, which indicate a complicating rudimentary or well-marked Basedow's disease—enlargement of the thyroid gland, inclination to perspiration, tremors, emaciation. This group of symptoms sometimes accompanies the chlorosis from the beginning to the end or it becomes temporarily manifest for several days or weeks in the course of the disease.

We will give a small table showing the frequency of the pulse in 214 cases of chlorosis. Those figures are recorded which were obtained at the height of the disease and at a time when the patients were quiet. The examinations were regularly made twice daily.

The pulse-rate	varied	between	60	and	70	in	3	cases.
"	"	"	60	"	80	"	9	"
"	"	"	70	"	80	"	27	"
"	"	"	70	"	90	"	24	"
"	"	"	80	"	90	"	49	"
"	"	"	80	"	100	"	53	"
"	"	"	90	"	100	"	14	"
"	"	"	90	"	110	"	5	"
"	"	"	100	"	120	"	4	"
"	"	"	110	"	120	"	6	"

Attacks of tachycardia with a pulse-rate of 130 and 160 occurred in 20 cases.

Cardiac Murmurs and Cardiac Dulness.—It is only in the milder cases that an examination of the heart gives normal results. In the more marked degrees of chlorosis blowing systolic murmurs are rarely absent; though of less frequent occurrence, we often find the area of cardiac dulness enlarged. There is neither doubt nor discord in reference to these facts. Since the earliest days of auscultation and percussion they have been constantly observed and the observation may be easily confirmed at any time.

Opinions diverge, however, in reference to the significance of these facts.

The explanation of these murmurs is more difficult and has been the subject of the greater discussion. In many respects they resemble the murmurs of mitral insufficiency; like these they have their greatest intensity over the apex and at the pulmonic cartilage; the first sounds may be either audible or inaudible. Over the aortic and tricuspid valves the murmurs are usually softer or entirely absent. There are cases, however, in which they are heard best in these situations. They sometimes differentiate themselves from the murmurs of mitral insufficiency by a certain tendency to variation; they are not always of the same strength. All teachers of physical diagnosis know that anemic murmurs easily heard to-day can not be expected to occur to-morrow. The murmurs may disappear with the chlorosis or they may remain for some after recovery from the disease. Diastolic anemic murmurs are rare.

The frequency of the murmurs is shown by the following compilation—Eichhorst[105] (38 cases) and v. Noorden (197 cases):

	Eichhorst.	v. Noorden.
I. Systolic murmur only at the apex	5 times.	40 times.
" " " pulmonic	2 "	12 "
" " " tricuspid	2 "	— "
" " " aortic	— "	1 "
II. Systolic murmur over two valves:		
Mitral and tricuspid	2 "	— "
Mitral and pulmonic	3 "	24 "
Tricuspid and pulmonic	4 "	2 "
Pulmonic and aortic	1 "	6 "
Mitral and aortic	— "	5 "
III. Systolic murmur over three valves:		
Mitral, tricuspid, pulmonic	8 "	2 "
Tricuspid, pulmonic, aortic	2 "	— "
Mitral, pulmonic, aortic	— "	23 "
IV. Systolic murmur over four valves	9 "	52 "
V. Clear tones in all situations	? "	30 "

The murmurs were loudest—

	Eichhorst.	v. Noorden.
over the apex	9 times.	76 times.
" pulmonic	21 "	62 "
" tricuspid	8 "	— "
" aortic	— "	7 "
not stated	— "	22 "

Statistics of Barrs:[106]

Of 205 cases of chlorosis, heart murmurs were heard in 115

at the base only	56	times.
" apex "	13	"
" base and apex	24	"
" " apex, and in the back	22	"

Statistics of Coley:[107]

Of 400 cases of chlorosis, all had murmurs at the pulmonic cartilage. Murmurs were also heard

at the apex	278	times.
" angle of the left scapula	123	"

The great number of hypotheses exist in reference to the systolic heart murmurs occurring in chlorosis. I will mention some without considering them in detail:

As a result of insufficient contraction of the papillary muscles, the mitral valves are not held tense, so that, though they are able to close, they are not able to vibrate regularly. This gives rise to a murmur instead of a tone.

As a result of relaxation and dilation of the left ventricle and of the insufficient contraction of the papillary muscles, which has already been mentioned, the mitral valves are not completely closed; a certain portion of the blood regurgitates, and this gives rise to a murmur, just as in true mitral insufficiency.

As a result of poor nutrition and relaxation, the heart muscle does not contract as powerfully and regularly as under normal conditions; a muscular murmur then takes the place of the muscular tone.

As a result of relaxation of the right ventricle, the tricuspid orifice is enlarged and a relative tricuspid insufficiency is produced. The systolic anemic murmurs are produced in this manner.

As a result of diminished pressure in the pulmonary artery and of relaxation of its wall, there is no marked systolic tension. The insufficient tension of the arterial wall causes it to vibrate, giving rise to a murmur instead of a tone.

The pressure in the pulmonary artery is so low that the semilunar valves open at the very beginning of the ventricular systole—*i. e.*, at a time when they should remain closed. The opening, however, is but a slit, and a stenotic murmur is consequently produced.

I could give a still larger number of attempted explanations. If we look over the text-books of physical diagnosis we find that scarcely two authors agree in their explanations of anemic cardiac murmurs. The special works[108] by Sehrwald, Bihler, Neukirch, Landerer, F. Reimers, Geigel, and v. Leube may also be consulted. Complete bibliographies of the literature are found in the monographs of Sehrwald and Bihler.

Although the individual explanations may be ever so interesting, ingenious, and necessary to the didactic lecturer, the only question of actual importance is whether the murmurs are indicative of a mitral insufficiency—*i. e.*, a regurgitation of blood from the left ventricle into the left auricle. With rare exceptions, all the standard authors answer this question in the negative. From the origin of auscultation to the present day, it has repeatedly been noted that the sequelæ which regularly follow a mitral insufficiency do not make their appearance in the overwhelming majority of cases of chlorosis in which systolic murmurs have been heard over the heart. In a disease lasting for many weeks or months the sequelæ would certainly make their appearance if there existed a regurgitation of blood with its damaging effects upon the circulation.

In the author's opinion, the condition of affairs is as follows: systolic murmurs in a chlorotic individual never justify the diagnosis of a valvular lesion, whether the murmurs are loud or soft, short or long, smooth or rough; whether they are heard over one, two, or three valves; whether they are more pronounced at the apex or at the base; whether they replace or accompany the first tone; or whether they are changeable or unchangeable. If we diagnosticate a valvular lesion (particularly a mitral insufficiency) in a chlorotic, we must do this not upon the basis of the murmur, but—the author would almost say—in spite of it. In the diagnosis of heart disease in a chlorotic it is best to leave the systolic murmurs completely out of consideration.

Mitral insufficiency surely occurs in chlorotic individuals, but this is nevertheless rare. It may be due to an endocarditis; then we have to do with a complication which is entirely independent of the chlorosis, the two affections having only accidentally attacked the same individual. Chlorosis itself never causes endocarditis. The only form of mitral insufficiency that may be dependent upon chlorosis is the so-called relative incompetency of the valves, which arises when there is marked relaxation and dilation of the left ventricle. It is easy to diagnose, for the heart is markedly enlarged, the apex-beat is displaced downward and to the left, and the pulmonic second sound is very loud. We must avoid diagnosing a cardiac dilation, however, when cardiac displacement is all that is manifest (see p. 394).

The signs of a mitral insufficiency are frequently present for but a short time. The following is a brief description of such a case:

The patient was a well-built girl, eighteen years of age, with well-developed breasts and normal sexual organs. For the past three months she had suffered from chlorosis, although she had previously enjoyed perfect

health. During the first week of observation loud anemic murmurs were heard over the heart, the area of cardiac dulness was enlarged upward and to the right, the apex-beat was in the fourth interspace in the mammary line, and both pulmonic sounds were louder than the corresponding aortic ones. During the second week of observation the cardiac dulness increased somewhat toward the right and considerably toward the left; the apex-beat advanced 1½ cm. (⅝ in.) outside of the mammary line and became palpable in the fifth intercostal space. The soft long-drawn-out murmurs, which had previously been heard at the apex and over the third rib, were replaced by a shorter and sharper blowing; the second pulmonic sound became louder at the expense of the first. The pulse-rate increased about 10–15 beats a minute (from 80–85 to 90–100). After about ten days more these phenomena had disappeared and the old state of affairs had returned. Frequent examination of the patient after she had recovered from the chlorosis failed to reveal the slightest abnormality by either percussion or auscultation. In this case it is positive that a temporary or so-called functional mitral insufficiency had occurred, probably as a result of dilation of the left ventricle.

From these and other observations and in accord with Gerhardt, Leube, Jürgensen, Eichhorst, and others, the fact that an incompetency of the mitral valves may develop in chlorosis must be emphasized, but this is nevertheless very exceptional. The usual changes in the heart of a chlorotic by no means justify the diagnosis of a mitral insufficiency. Particular caution must be observed if the diagnosis is based upon the extent of the cardiac dulness. In numerous cases of chlorosis, particularly when the patients have been confined to bed for a long time, the area of cardiac dulness is enlarged to the right, to the middle of the sternum, to its right border, or even beyond it. It is, however, not correct to consider this extension of the cardiac dulness as a sign of cardiac dilation, because an exact examination shows that the lower border of the right lung is higher than normal and that the cardiac dulness begins at the third rib or in the third intercostal space. In other words, the heart is not as well covered by the lungs as is normally the case. This is not due to the heart pushing the lungs to one side, but to the fact that the lungs have drawn themselves away from the heart—they have become smaller. The retraction of the borders of the lungs is doubtless due to the superficial breathing of the chlorotics. This is shown by the fact that breathing exercises cause a descent of the lower borders of the lungs and a diminution of the area of cardiac dulness within a few days. A frequent phenomenon of auscultation is also rendered intelligible by this marked retraction of the lungs. Not rarely in chlorosis the first and second pulmonic sounds are louder than normal, in contradistinction to mitral lesions in which the second tone is alone accentuated. This phenomenon in chlorosis is explained by

the fact that the retraction of the air-containing tissue of the lungs exposes the pulmonary artery to a more marked degree than the aorta, the sounds of which serve as a comparison. The exposure of the pulmonary conus arteriosus may be so considerable that an active pulsation is seen and felt in the third, and even in the second, intercostal space. This retraction of the pulmonary borders not only stimulates a dilation and hypertrophy of the right ventricle, but also an enlargement of the left. The apex-beat is displaced to the left and—to be well noted—not downward, but upward. In cases of retraction of the lungs, the apex-beat is felt in the fourth instead of the fifth intercostal space (v. Noorden,[109] Fr. Müller[110]). The topographic relations between the heart, lungs, and chest-wall are consequently the same as those which have long been recognized as the consequence of a high position of the diaphragm. We should bear in mind the discussions upon enlargement of the heart during pregnancy. It is not unlikely that a neglect of these topographic relations has given rise to the teaching that chlorosis is frequently associated with a dilation of the left ventricle. Strange to say, most of the earlier authors who considered the variations in the area of cardiac dulness in chlorosis (Th. Stark[111] in particular) paid no attention to the retraction of the lungs. Th. Jürgensen, alone, long since recognized the importance of this pulmonary retraction for the critical examination of the chlorotic heart, and caused his views to be published in the noteworthy discussion of Th. Loock.[112] The subject has been taken up again recently and worked out by a number of authors (Wallerstein,[113] Th. Rethers,[114] Stintzing,[114] v. Noorden,[109] Fr. Müller[110]).

As the authors were about to send this manuscript to the printer, the work by E. Grunmach, in reference to the importance of the Röntgen rays in internal medicine was received.[1] By means of the x-rays, Grunmach established the fact that in 4 chlorotics the heart lay with its entire transverse diameter upon the diaphragm, which was unusually high. The heart was not enlarged, but simply displaced. After the disappearance of the chlorosis the heart resumed its normal position. The observations of Grunmach furnish the most brilliant confirmatory evidence that in chlorosis the heart is only apparently enlarged.

Finally, mention must be made of the rare occurrence of diastolic cardiac murmurs. In contrast with the systolic murmurs, they have their seat of greatest intensity to the right of the sternum, over the aorta. They consequently simulate an aortic insufficiency. It is, however, very easy to exclude these murmurs (Litten,[115] Dehio,[116] Duroziez,[117]

[1] *Therapeut. Monatshefte*, 1897, No. 1.

Sehrwald,[108] Sahli[118]). Eichhorst[119] alone considers the possibility of a relative functional insufficiency of the semilunar valves. Others, Sahli in particular, say that the murmur is transmitted from the great veins of the neck.

Opinions vary greatly in reference to the frequency of accidental diastolic cardiac murmurs. Many regard them as extremely rare; v. Leube,[108] for example, recently stated that he had never heard such a diastolic anemic murmur over the heart. In 180 clinical histories of the Second Medical Clinic in Berlin, the accidental diastolic cardiac murmur is mentioned 7 times; 3 of these cases the author observed and repeatedly demonstrated to colleagues and students. During the last three years he has heard accidental diastolic murmurs in 4 other chlorotics. The murmurs were always loud and distinct, and their perception required no great amount of skill. They were undoubtedly accidental anemic murmurs, since they always disappeared when the chlorosis improved and because no other signs of aortic insufficiency could be discovered, in spite of careful investigation. The most forcible proof, however, was furnished by a small experiment that has been successful in the last 6 cases coming under the author's observation. If pressure is made upon the lower portion of the internal jugular vein, the diastolic cardiac murmur immediately disappears. This, consequently, shows the correctness of Sahli's explanation.

According to the author's clinical records, diastolic anemic murmurs occur only in severe cases of anemia; the murmur disappears as soon as the anemia improves. The murmur is heard loudest just below the sternoclavicular articulation; further downward it becomes softer, and then attains a second maximum at the aortic cartilage; from this point the murmur may be followed to the middle of the sternum or even to its lower third. To the left of the sternum the murmur is audible only at the third costal cartilage; it is rarely heard at the apex, and in this situation is always very soft. The murmur is much louder when the patient sits or stands than when she is recumbent.

ARTERIES, VEINS, AND CAPILLARIES.

Angiospasm and Angioparesis.—In the section upon General Symptomatology it was pointed out that changes in the vascular tone are extremely common in chlorosis. The majority of the consequent disturbances are trivial and unimportant. They consist of abrupt changes in the sensations of heat and cold, and are dependent upon the great irritability of the smaller arteries and capillaries. More marked degrees of angiospasm and angioparesis are productive of much discom-

fort and even pain. As usual, the phenomena are more marked in the peripheral portions of the body. Among these symptoms are the rapid chilling of the feet, of the fingers, of the hands, and of the tip of the nose. The sensation is not always simply one of cold, but may be combined with considerable pain. The angiospasm lasts from a few minutes to a half-hour. Sometimes they appear whenever the cold air strikes the bare skin; in other instances they show a certain capriciousness. This is particularly true of the so-called dying finger (digitus semimortuus, local asphyxia), which repeats itself in many chlorotics for weeks and months at a time—often at the same hour of the day—although every exposure to cold is carefully avoided. The opposite condition, temporary congestion of the terminal phalanges, combined with moderate pain, decreased tactile sensation, and paresthesias in the fingers, is rarer; these conditions are to be attributed to the so-called erythromelalgias and to the acroparesthesias described by Fr. Schulze.

Of 230 chlorotics,

71 complained of chilliness of the hands or feet,
10 suffered with the so-called digitus semimortuus,
6 " " erythromelalgia, and
18 " " chilblains of the feet during the winter.

The Pulse.—There is nothing typical about the pulse in chlorosis, either when examined with the palpating finger or with the sphygmograph. In this respect we agree with Hayem [120] and others. We find chlorotic individuals with small, with normal, and with large pulse-waves. In the great majority of cases of pure chlorosis, particularly in the severe forms, we have encountered a large soft pulse with a suggested or well-marked dicrotism. Numerous sphygmographic examinations gave the same result. Many of the sphygmograms showed the same characteristics as the pronounced dicrotic fever-pulse: considerable height, steep ascent, acute apex, a large delayed second (so-called reflected) wave, and absence or flattening of the so-called elastic vibrations. Similar sphygmograms have been described by Lorain,[121] Fr. Müller (Jacoby's dissertation [46]), Eichhorst,[122] and others. As previously stated, the large soft pulse with a tendency to dicrotism is not present in every case; according to the author's observations, extending over many years, it is most frequently found in the early stages of severe chlorosis, particularly in girls who are strong, well nourished, and fully developed.

The quality of the pulse just described indicates that the resistance offered to the blood by the arterial wall is abnormally diminished, or, in other words, the tension of the arterial wall is decreased. It con-

sequently follows that other phenomena are occasionally observed which result from diminished arterial tension and lessened resistance.

In the first place, the occurrence of a capillary pulse in the hyperemic skin of the forehead is worthy of note; the author could repeatedly demonstrate this in every teaching term, in the courses upon physical diagnosis (Rethers [114]). More rarely the pulsating movements pass through the capillaries and reach the veins. This was first observed by Quincke.[123] Venous pulsation, when present at all, is most easily recognized in the background of the eye. In 46 of my clinical histories there are accurate records of ophthalmoscopic examinations; venous pulsation is mentioned in 3 instances.

A double sound in the femoral artery also owes its origin to the arterial relaxation. This is first mentioned in Jacoby's [48] dissertation; the text-books on physical diagnosis have since recognized this phenomenon. From personal investigations, the double sound is quite common in severe cases; when present it is easily perceived, being even more readily heard by beginners than the double sound of aortic insufficiency. The second sound is separated from the first by a considerable interval of time, which is longer than in other instances of double sounds in the femoral artery (aortic insufficiency, lead colic, mitral stenosis). With the aid of the "marking method" of Martius, the author was successful in 1 case in proving that the first sound was produced by the primary wave, and that the second sound was due to the reflected wave. This is not the case in aortic insufficiency, the second sound in this instance being dependent upon a secondary elevation which is much nearer to the primary apex of the curve (Pribram [124]). The double sound in the femoral artery in chlorosis has the same significance as the dicrotic pulse; they both show that the arterial tension is abnormally decreased, and that the reflected wave is able to produce a marked and abrupt dilation of the arterial tube.

Reference has been made to vascular sounds and murmurs in 130 of our clinical histories. The double sound in the femoral artery is mentioned 21 times. These cases were, almost without exception, severe, and the radial pulse was usually described as quick and dicrotic.

Although the author is by no means inclined to consider so-called sphygmomanometry as anything more than a clinical amusement, it might also be stated that measurements of the blood-pressure have furnished results which completely agree with the above facts. Bihler [108] found, by means of v. Basch's apparatus, an average blood-pressure equal to 77 mm. of mercury, in chlorotic patients upon admission to the hospital; at the conclusion of the treatment the average pressure was

86 mm. His apparatus recorded 90–120 mm. of mercury as the normal pressure in girls of the same age. Euren [125] seems to have arrived at similar results.

The Veins.—Venous Murmurs.—Of the pathologic phenomena in the venous system, the murmurs have claimed the greatest amount of consideration (venous hum, bruit du diable). The venous hum is most frequently heard over the internal jugular vein at the root of the neck, either on both sides or only on the right. The murmur is favored by the erect position; the intensity of the murmur is either always the same or it increases during inspiration, or more rarely during the diastole of the heart. Sometimes a similar murmur is heard over the femoral veins also; in all the cases personally examined in reference to this point the venous hum in the femoral vein disappeared during standing.

Venous murmurs were first encountered in anemic individuals, and formerly we simply spoke of anemic venous murmurs. The expression is not correct, because a venous hum may be heard in the jugular vein in many other patients and even in healthy individuals. In these latter instances, however, the head must usually be turned or tilted in order to make the murmur perceptible. In anemic individuals and particularly in chlorotics the murmur is also heard when the head is held erect and when a pressure which could cause a constriction of the jugular vein is avoided. When this acoustic phenomenon is well developed there is a corresponding thrill which is distinctly perceptible to palpation, and which has been compared to a stream of sand flowing rapidly beneath the finger.

The venous hum certainly has some connection with the fact that at the lower portion of the internal jugular vein the blood streams out of a smaller into a larger vessel. Similar conditions exist in the femoral vein just below Poupart's ligament. According to the laws governing the movements of fluids, the murmur must arise more easily when the vein contains a lessened amount of blood, since the difference between the transverse diameters of the vein and of its inferior portion is then more marked. It is very doubtful if this condition will suffice for the explanation of the particular intensity and frequency of the venous hum in chlorotic individuals, since, so far as we are able to determine by sight and touch, the veins of chlorotics are completely filled with fluid. In chlorosis the condition is one of oligochromemia and not one of oligemia. Since venous murmurs are neither so loud nor so frequent in any other disease, there must be some other coöperative cause in chlorosis. The quality of the blood is probably a favoring factor,

since thinner and lighter blood is better adapted to the formation of whirls.

There are many statistics in reference to the frequency of the venous hum in chlorosis, but all are not equally valuable, since the severity of the disease and the position of the head during auscultation had not always been considered. The author has made brief notes upon 62 cases, which he has demonstrated in courses upon physical diagnosis during the last five years. Of these, 49 are designated as "severe cases of pure chlorosis"; with the head erect and the patient in a sitting posture the jugular murmur was bilateral 26 times, right-sided alone 19 times, left-sided alone in 1 case, in 3 instances no murmur could be heard, and in 4 a venous hum was present over the femoral veins. There are also recorded 13 cases as "milder cases of pure chlorosis"; among these there was 1 with a bilateral jugular murmur, 5 with a right-sided murmur, but none with a venous hum in the femoral vessels.

In 130 out of 250 clinical records, statements in reference to auscultation of the vessels are found. The venous hum in the neck is mentioned 95 times, and in 12 instances its absence is expressly emphasized. The murmur in the femoral veins was present 14 times.

The following statistics may also be quoted:

Eichhorst[126]: Bilateral venous murmurs in the neck in 50 per cent., unilateral murmurs in 25 per cent. of all cases of chlorosis.

Richardson[127]: Right-sided jugular murmur in 33 per cent., left-sided in 6 per cent., and bilateral in 11 per cent. of all cases of chlorosis.

Crook[128]: Jugular venous murmurs in more than 90 per cent. of all cases of chlorosis; present in 6.95 per cent. of healthy women.

[The position of the patient is of some importance. Venous murmurs are more frequently present when the patient is in an upright position.—Ed.]

Thromboses.—Far more important than the venous murmurs, which have scarcely any diagnostic significance, is the tendency to the formation of thrombi in the veins. If we consider the unusual frequency of chlorosis in comparison with the occurrence of thrombosis, this complication must be regarded as unusual. But when we remember how rare thrombosis is at the age of the majority of chlorotic patients—excluding severe cardiac and acute infectious diseases—it becomes apparent that the tendency to thrombosis is far more marked in chlorotics than in other girls of the same age, whether they are healthy or affected with some other disease. Trousseau seems to have been the first to point out the occurrence of this complication (Werner[129]). About 20 cases published separately were collected by Proby,[130] and later com-

bined with the newer statistics of Kockel.[131] There are also a number of cases which either escaped these authors or appeared after their publications. Such are the cases of Laache,[132] Tuckwell, Hüls, Eichhorst, v. Noorden-Rethers, B. Krönig, H. Bergeat, Villard, LeSage, H. Mildner, Osswald, J. Loewenberg, Hayem, and Guinot. The author does not claim to have completely quoted the literature, but the number of publications bears witness to the fact that thrombosis is not rare in chlorosis. The number still remains proportionately large if we regard some cases of thrombosis as due to the concomitant complications instead of counting them as true chlorotic thromboses—for example, Villard's case complicated with influenza, Mildner's case complicated with suppurative pyelonephritis, and LeSage's case complicated with suppurative peri-oöphoritis.

In 230 of the authors' clinical histories thrombosis of the veins is recorded 5 times. In every instance the thrombosis was located in the veins of the lower extremities. These veins were likewise most frequently affected in the cases previously published; the veins of the arm were not involved as often as the brain sinuses. This is always a grave complication and is followed by incalculable danger. Gangrene of the hand, with the loss of several fingers, has been described by Tuckwell, and Laurencin[133] reported a fatal case from embolism of the pulmonary artery. The fatal cases are much more frequently due to thrombosis of the cerebral sinuses. The great danger of thrombosis is shown by the fact that the majority of post-mortem records of cases of chlorosis give thrombosis of the veins or its sequelæ as the cause of death (Bollinger, Kockel, Proby, LeSage, Loewenberg).

A description of the details is unnecessary, since the thrombosis presents no variations from the process in other conditions. The course and termination will depend upon the localization of the thrombus (contrast the femoral veins with the brain sinuses!), upon the nature of the thrombus, and upon the presence or absence of embolic processes.

In some instances the thrombus has undoubtedly been of an infectious nature (Villard, Mildner), but these cases were complicated by infectious diseases which themselves favored the development of infectious thrombi. In most of the other cases it is expressly emphasized that the thromboses were not infectious, the proof offered being partly clinical and partly bacteriologic. Proby was unable to demonstrate bacteria in 4 of his cases, and J. Loewenberg had a similar experience. The author once punctured a thrombosed saphenous vein, with a negative result (microscopic preparation and agar plate). In spite of this, he thinks it probable that micro-organisms have something to do with

chlorotic thrombi. This is particularly evidenced by the fever, which was not absent in any of the 3 cases. Two of the patients had temporary elevations of temperature during the first few days of the thrombosis; the third, in whom the vein was punctured upon the sixth febrile day, had fever of a remittent type for ten days, which several times reached 40° C. (104° F.). Fever is also recorded in numerous cases by other authors.

In addition to the supposition of a bacterial origin, there are still other hypotheses in reference to the geneses of these coagula. Eichhorst[132] seeks the cause in changes in the intima; Birch-Hirschfeld[134] and Kockel[131] believe that chlorotic blood has a greater tendency to coagulate, and they associate this with the increased number of blood-platelets (see p. 378). Against this view we would call attention to the fact that chlorotic blood ordinarily does not coagulate rapidly; on the contrary, we have been surprised at the slow formation of the coagulum in chlorotic blood withdrawn from a vein. It is true we did not make this examination in cases affected with thrombosis.

There is much that is not clear and the subject requires further investigation. If the literature of the subject is desired, it may be found in the works of Proby and of J. Loewenberg.

[Leichtenstern[1] has studied the occurrence of venous thrombosis in 1658 cases of chlorosis. Thrombosis positively occurred 11 times, and probably in mild form in a few other instances. He finds 86 cases referred to in the literature, of which 48 affected the lower extremities and 29 the cerebral sinuses. Among 52 affecting the lower extremities, pulmonary embolism occurred in 10.—Ed.]

Edema.—If we compare chlorosis with other diseases of the blood, the occurrence of edema in chlorotic individuals seems to be rather infrequent. Marked edemas with involvement of the large serous cavities are never observed. Fleeting edemas, on the contrary, are not so uncommon. The most frequent form is the edema of the feet, which occurs in chlorotics who must stand a great deal, such as servant girls, cooks, and factory hands. The swelling comes on in the daytime, to disappear again during the night. It is only in exceptional cases that the feet are still swollen in the morning. Of 218 chlorotics treated in the hospital, 24 (12 per cent.) had edema of the feet upon admission and for several days subsequently; 20 of these lost their edema after a few days' rest in bed, and remained free from it when they walked about the ward. The swelling of the feet lasted a long time in but 4 patients. Edema of the feet is much rarer among private patients than among

[1] *Munch. Med. Woch.*, Nov. 28, 1899.

the girls and women who are treated in the public hospitals. My notes of private cases show that about 6 per cent. are affected in this manner. In addition to edema of the feet, patients with pure chlorosis may rarely present a slight swelling of the eyelids, which tends to be more pronounced in the morning hours. When a chlorotic is seen with such an edema of the eyelids, a suspicion of nephritis is at once awakened. This suspicion is not always justified, since I can recall several cases in which the repeated daily examination never resulted in the discovery of albumin.

Less known and less considered than the occasional appearance of fleeting edemas is the fact that many chlorotics collect considerable quantities of water in their tissues without the production of visible and palpable circumscribed edematous swellings. The blood-plasma may retain its normal amount of water. The proof of the accumulation of water in the tissues is based upon the observation that many chlorotics rapidly lose weight and excrete large quantities of urine as soon as they are placed upon a diet that is proportionately poor in water. This point is of therapeutic interest and will be referred to later.

THE RESPIRATORY ORGANS.

FREQUENCY OF RESPIRATION.

Repeated reference has been made to the condition of the respiratory organs in the preceding sections and all the essential points have been considered. I would recall the excited breathing and the sense of dyspnea and oppression which follow upon muscular exertion. The breathing may frequently be accelerated without any preceding physical exertion.

To obtain a general idea of the frequency of respiration in chlorosis we will give the following table, which is based upon 140 clinical histories from the Second Medical Clinic of Berlin. The patients were examined twice daily for many weeks, and the numbers recorded were those most frequently observed.

At the height of the disease the average number of respirations in a minute was in

10 cases less than	20	5 cases less than	24–30
7 " "	18–22	3 " "	26–30
8 " "	18–24	1 " "	26–32
66 " "	20–25	3 " "	26–34
17 " "	22–28	1 " "	28–32
12 " "	24–28	7 " always more than	30

Since almost all the observations were made with the patients in bed, the majority of these figures indicate a considerable increase above the

normal respiratory rate. It is more than accidental that among the cases with a greatly increased respiratory rate there were many that presented the previously described characteristics of a high position of the diaphragm. In other words, the breathing was both accelerated and superficial. In other cases these qualities were not associated—*i. e.*, the respiratory rate was normal, although the borders of the lung were retracted. The diagnostic significance of retraction of the lungs has been considered at p. 394.

HYSTERICAL TACHYPNEA.

In rare instances tachypnea may occur in actual attacks, which last for hours and tend to recur frequently. They are comparable to the attack of paroxysmal tachycardia, and are sometimes observed to alternate with this affection. The number of respirations may be increased to twice or three times the normal rate. The sensation of dyspnea is, however, wanting. We can scarcely regard the attacks of tachypnea as a phenomenon intimately associated with chlorosis; they are rather one of the many nervous symptoms which naturally make their appearance in girls predisposed to hysteria. Upon one occasion, after a chlorotic had had her usual attack of hysterical tachypnea, the author saw all the chlorotics (5) and several other girls in the same ward seized with similar attacks. This was a marked example of that psychic contagion which is so frequently observed in hospital wards.

Frequently recurring attacks of tachypnea are recorded 13 times in 230 clinical histories. The respiratory rate was usually above 40 and sometimes reached 50 and 60. In some instances the paroxysms occurred at intervals of several days; in other cases they occurred in groups for two or three days and then disappeared to return later. In about 10 other cases the number of respirations varied considerably (between 18 and 30), so that they could not be considered as actual paroxysms of tachypnea.

HYSTERICAL APHONIA.

The author once saw functional aphonia occur in much the same manner as that just mentioned in reference to tachypnea. It spread from one patient to many inmates of the ward, and attacked many chlorotics. A functional aphonia which rapidly disappears is not rare in chlorosis. In but 3 instances out of 230 cases was this symptom of long duration, or did it play any important rôle in the symptomatology. It is not a phenomenon peculiar to chlorosis, but it is associated with a complicating predisposition to hysteria.

PULMONARY TUBERCULOSIS.

We know of no other pathologic disturbances of the respiratory organs which are dependent upon chlorosis or favorably influenced by the disease. Particular emphasis is to be placed upon the fact that tubercular affections of the lungs and bronchial glands in young people frequently produce a condition which is very similar to the clinical appearance of chlorosis (chloro-anemie tuberculeuse, pseudochlorosis). We are not yet in a position to understand why the very beginning of tubercular infection is so frequently followed by anemia, before the other general symptoms become manifest; it is probably due to the absorption of toxins from the tubercular areas, which retard blood-formation or favor blood-destruction. At the present time the generally accepted idea is that tuberculosis is the primary disease, while the anemia is a secondary affection. This is in opposition to the old view formerly championed by Immermann,[1] that chlorosis predisposes to pulmonary tuberculosis. All sorts of efforts have been made to differentiate true chlorosis from tubercular pseudochlorosis. The separation is easy if, in addition to the anemia and the symptoms immediately dependent upon it, there are present other signs which are indicative of tuberculosis. Among these signs we would mention: Changes at the apices of the lungs, tubercle bacilli in the sputum, fever, considerable emaciation in spite of a liberal diet, and pronounced tubercular antecedents. The writer can not agree with those authors (Hérard, Cornil, and Hanot) who would diagnosticate or exclude tuberculosis from the particular condition of the blood or from a special grouping of the symptoms. Unless the additional symptoms mentioned above are present, he does not believe that such a diagnosis is always possible. It has been observed that in girls with concealed tubercular foci, a true chlorosis can develop independently of the tuberculosis (Hayem [135]). Upon the other hand, tuberculosis may sometimes produce a condition of the blood and a group of general symptoms that can not be differentiated from chlorosis without a grave violation of the clinical evidence. As is so frequently the case, particularly in diseases of the blood (in grave or pernicious anemia, for example), the contrast is not to be found in the symptomatology, but in the etiology. It is of the greatest importance to consider the etiology and to endeavor most conscientiously to separate the cases of genuine chlorosis from those conditions which present the symptom complex of chlorosis, but which are due to tubercular intoxication. The two conditions vary widely in their prognosis and therapeutics, and the author regards their differential diagnosis as one of the most difficult and responsible tasks encountered in medical practice.

THE DIGESTIVE ORGANS.

SUBJECTIVE DISTURBANCES. NERVOUS DYSPEPSIA.

With the exception of the changes in the blood, no other system of organs so frequently presents pathologic phenomena in chlorosis as does the digestive apparatus. Until a few years ago the subjective disturbances demanded the greater amount of attention.

The following description must be preceded by the statement that of the manifold digestive disturbances of chlorosis there is not a single symptom the presence of which may be definitely expected in any individual case. Many chlorotics remain free from digestive troubles throughout the entire course of the disease; some patients have temporary complaints which may be frequently repeated, but which are never the chief source of annoyance; in a third and quite large group the digestive symptoms play the chief rôle among the discomforts of the patient.

At this place a few statistics might be quoted.

Of 157 chlorotics, dyspeptic troubles of the most varied nature, either alone or in association with other symptoms, formed the chief complaint in 49 (31.2 per cent.) of the patients. In a much larger number there were temporary disturbances of the gastric and intestinal functions, but these did not form an essential part of the discomforts of the patient.

The frequency of individual symptoms was as follows:

Of 192 chlorotics, 75 (39 per cent.) complained of gastric pain; 30 (15.1 per cent.) were troubled by vomiting during the course of the disease.

Of 216 chlorotics, 9 (4.1 per cent.) had gastric ulcers.

Of 182 chlorotics, 68 (31.1 per cent.) suffered from constipation, 9 (4.9 per cent.) had diarrhea, and 4 (2.2 per cent.) had alternate attacks of constipation and diarrhea.

Gastric Pain.—Pain is the most troublesome of all the subjective disturbances and is the basis of the most frequent complaint. Abdominal pain in chlorosis, which is correctly or incorrectly designated by the patients as "pain in the stomach," is due to different causes. It is very important to determine the cause of the pain in every individual case, because it is usually easy to relieve it when the actual condition of affairs is recognized.

Tenderness in the Epigastrium, just Below the Xiphoid Cartilage.—This pain is elicited during examination when the finger is

pressed upon the spot just indicated; it also becomes noticeable when the individual bends forward so that the corset steels are pressed against the intercostal angle. This variety of pain has no diagnostic importance; it is encountered in many healthy individuals and is particularly frequent in very excitable nervous women. It reveals the existence of a general hyperesthesia rather than the presence of any pathologic process in the abdominal cavity.

Tenderness and Pain Throughout the Entire Gastric Area.—This annoying symptom is usually more troublesome after eating than when the stomach is empty; even in the latter condition, however, it is not entirely absent. It depends upon hyperesthesia of the gastric nerves and does not allow of any conclusion in reference to the digestive process.

Pain After Eating.—These pains may vary in their significance. Sometimes they are the result of hyperesthesia; in other instances they are due to the hyperchlorhydria of the gastric juice, which is very frequent in chlorosis. Similar pains are experienced by other individuals who suffer from an excessive secretion of hydrochloric acid. In a third and much smaller group of patients the pains are caused by a gastric ulcer. In all cases the gastric pains are largely dependent upon the quality of the food. The more irritating the mechanic and chemic qualities of the diet and the more abundant the meal, the more pronounced will be the annoyance. Rest after eating, particularly in the dorsal position, tends to lessen the severity of the pain. If a gastric ulcer is present an area of circumscribed tenderness corresponding to the location of the ulcer can usually be found.

Colicky Pains or So-called Cardialgias.—These frequently end in vomiting, and from their character are to be referred to spasmodic contractions of the involuntary musculature. Some of these attacks are due to a closure of the pylorus and true gastric spasm. They may be present, although no other objective disturbance of the stomach may be recognized. They more frequently occur as a complication of gastric ulcer or of gastric atony. During the attack marked peristaltic movements may sometimes be seen and felt over the stomach. The abdominal walls are usually so contracted, however, that we are unable to perceive any of the intra-abdominal movements. When there is a change in the shape and size of the stomach, it sometimes happens that the pylorus becomes temporarily bent at an acute angle with the remaining portion of the stomach; spasmodic contractions then occur and give rise to cardialgia. It very frequently happens that the colicky pains do not originate in the stomach at all, but in the transverse colon.

The colic of the large intestine in chlorosis may be entirely independent of fecal stasis or of an angulation of the intestine. The author has repeatedly observed it in chlorotics whose bowels were regularly evacuated, in whom hard fecal masses could never be palpated in the transverse and descending colons, and whose abdominal organs were normally situated. During the attacks the transverse colon could be felt as a hard, sensitive cord, which rapidly changed its consistence beneath the palpating finger. The attacks were repeated daily for some time; in some instances they ceased gradually, while in others they disappeared abruptly. Warm applications during the attack and the regular administration of extract of belladonna had a decidedly favorable effect.

From the statements of the patient it is scarcely ever possible to ascertain with certainty the cause of the attacks of pain. This can be discovered only by an exact investigation which can not be carried out in the physician's office, but which requires careful clinical observation. We find "cardialgic attacks" recorded 17 times in 250 cases of chlorosis.

Costalgia.—Tenderness at the costal margin, usually left-sided, is quite frequent in chlorosis. It is usually most marked at the end of the eleventh rib and between the parasternal and mammary line. The author must completely agree with O. Rosenbach when he refers this variety of pain, without exception, to the influence of the corset. Tenderness of the costal border is never found in girls who are sensibly dressed. If the corset pressure is marked an actual periostitis may be produced, which makes itself manifest by the thickening of the periosteum. The costal pain is not always present. It is not felt in the erect position, in spite of tight corsets, but it may be elicited by bending forward or to one side; by an increase of the intra-abdominal pressure; by overloading the stomach, or by flatulence. If the rib affected with periostitis is pressed upon the patient cries out with pain. The most effective therapy is the substitution of a well-fitting corset for the tight one. In a few days the tenderness will usually diminish and then gradually disappear.

Nervous Dyspepsia—Craving for Acids.—Since our knowledge of the pathology of the digestive organs has been so greatly extended during the last twenty years, more stress has been laid upon the demonstration of objective changes in chlorosis, as well as in other diseases. This is of particular importance, since it is quite common for obstinate and severe digestive symptoms to be present without any recognizable change in the motor or chemic functions of the gastro-intestinal tract. In view of the disproportion existing between the

subjective and objective symptoms, it is frequently necessary to exclude actual diseases of the digestive organs, and to speak of "nervous dyspepsia." In chlorotics, whose nervous systems offer such manifold signs of pathologic irritability, we should naturally expect something of this kind. As a matter of fact, the number of chlorotic individuals with pure nervous dyspepsia is not small. The appetite is whimsical or lost, there is a sensation of weight in the epigastrium after eating, which may amount to actual pain, tenderness in the lateral abdominal region, and a marked desire either for sour foods or such acid-neutralizing substances as chalk. Conscientious examination and long-continued observation, however, show that the stomach is normal, both in size and position; the motor power, secretion of acids, bowel movements, and absorption of nutritive material are also normal in every respect. If much attention is paid to these complaints, or if an endeavor is made to elicit all the details possible in reference to them, we run the risk of increasing the difficulty, as is the case in many hysteric or hypochondriac individuals. If we examine the patient carefully, and, instead of considering these symptoms, demand an increased amount of work of the stomach and intestines, the disturbances often disappear in a short time, and not a symptom remains to recall their previous existence. This has been the repeated experience of those who do not always follow the beaten paths in the treatment of gastric troubles, and who do not confine their efforts simply to limitations of the diet in every case in which there is a disturbance of the gastric or intestinal activity. Such men have become convinced that the functional activity of the digestive apparatus suffers much less in chlorosis than the exaggerated warnings of many authors would lead us to believe. In order to show the incongruity between the sensations of the patient and the actual state of affairs, the author may be allowed to mention some investigations which he carried out in patients who had a marked craving for acids. Many authors, including O. Rosenbach,[136] still believe that the desire for acidulous foods (vinegar, lemons) in chlorosis is an infallible symptom of the deficient production of hydrochloric acid. In 6 chlorotics who exhibited this craving for acids to a marked degree, the author washed out their stomachs repeatedly and found in all cases not only normal, but even surprisingly large, amounts of hydrochloric acid: (Hyperacidity, minimum 0.28 per cent., maximum 0.37 per cent. HCl; organic acids absent.) Instead of acids, the last 2 patients coming under his observation were given small amounts of calcium carbonate at frequent intervals throughout the day, and the craving for acidulous substances immediately disappeared.

It may also be shown that in many other respects the subjective symptoms of chlorosis are not always dependent upon definite disturbances of function. In some cases there may be a certain hyperesthesia of the gastric and intestinal nerves, which is responsible for the transmission of exaggerated sensations to the cerebrum (Rosenheim[137]). In other instances a series of painful and tender areas may be found which G. Sticker[138] has recently described as characteristic of hysteria.

If, in accord with many of the older authors and fully armed with the modern technic of investigation, the author should claim that many chlorotics have subjective digestive disturbances without any actual impairment of the digestive function, he must, on the other hand, still more sharply emphasize the fact that actual disturbances of the digestive organs are observed in chlorosis, and that it is still doubtful whether these disturbances simply accompany the disease, whether they are the results of chlorosis, or even whether they are able to produce the affection.

THE POSITION OF THE ABDOMINAL ORGANS—THE CORSET.

The old and fruitless struggle of physicians against the unreasonable dress of women, particularly against the corset, has been recently renewed from the standpoint that a constriction of the lower thoracic aperture and a downward displacement of the abdominal organs lead to chlorosis. The connection between cause and effect has been explained in a number of different ways. O. Rosenbach[139] regards the corset as an actual hindrance to respiration, which is responsible for an insufficient supply of oxygen ; the lack of oxygen is the cause of the destruction of hemoglobin and anemia. The further observation of Rosenbach,[8] that the corset compresses the stomach and hinders the ingestion of sufficient food, is more correct. Nevertheless, this is not a sufficient explanation for the origin of such a typical disease as chlorosis. Deficient nutrition may be followed by disturbances of growth, emaciation, and anemia, but these sequelæ by no means resemble chlorosis.

The studies of Meinert[140] are much more profound and worthy of attention than are Rosenbach's aphorisms concerning the relations between the corset and chlorosis. At the Tenth Congress of the Pediatric Society (Nuremberg, 1893), Meinert reported the results of inflating the stomachs of chlorotic individuals. The inflation was accomplished in some cases by the insufflation of air, and in others by the development of carbonic-acid gas. When the inflation was marked, it was found that both the upper and lower boundaries of the stomach

were lower than normal. From the numerous illustrations the actual conditions of affairs seems to have been a downward displacement of the pars pylorica. For this condition Meinert employs the term adopted by Glénard, "gastroptosis"; recently the word "gastrokateixia"—displacement of the stomach—has been suggested (C. A. Meltzing[141]). The degree of the gastric displacement was quite considerable in some cases; we find in the dissertation just mentioned, as well as in the later publications of the same author,[142] numerous cases in which the greater curvature of the stomach extended a hand's breadth below the umbilicus. Meinert designates the constricting effect of the corset as the cause of the gastroptosis. Supposing the observations to be correct, there was really no other apparent cause. The patients were, almost without exception, very young girls at the age of puberty, with relaxed abdominal walls. Meinert expressly states that in his practice it was frightful to observe the great extent of the popularity of tight-fitting corsets among this class of young women. The further train of thought which Meinert followed concerning the causal relations between gastroptosis and chlorosis is worthy of note. The changed position of the stomach causes a tension and irritation of the sympathetic nerves—of the solar plexus particularly—which control the distribution of blood and the formation of hemoglobin in the spleen. This latter organ is influenced by the damage done to the sympathetic plexus, and anemia is consequently produced. The pathologic irritation of the sympathetic plexus is also responsible for the spontaneous epigastric pain, which is increased by pressure and which is so frequently complained of by chlorotics. He also traces such symptoms as hyperhidrosis, facial acne, and seborrheal eczema to the abnormal irritation of the abdominal sympathetic. We see that Meinert's teaching consists of two parts, which are to be sharply separated: The first part is composed of anatomic facts which demand confirmation on account of their importance; the second part is made up of hypotheses and theories which lead us through obscure paths and constantly require fresh hypotheses for their support. There has been no lack of confirmatory, as well as of contradictory, reports. Among those agreeing with Meinert we find the work of J. Boudou[143] and also the article by Ageron[144] in the Fourteenth Congress for Internal Medicine. The works of Martius-Meltzing,[145] Leo-Brüggeman,[146] and of A. Huber[147] vary in many important respects. The following questions were to be answered:

1. Is the simultaneous occurrence of chlorosis and gastroptosis as common as Meinert claims, and is the gastroptosis so much more common in chlorotics than in other young non-chlorotic individuals of both

sexes that we may assume the existence of an intimate connection between chlorosis and gastroptosis?

2. Were Meinert's cases actual instances of gastroptosis, or are the results of his inflations to be otherwise explained?

In 2 cases of pronounced chlorosis Huber failed to find "any indication of gastroptosis"; no statements were made in reference to his method of examination. Martius and Meltzing examined the stomach by transmitted light and found that "the transilluminated stomach filled with water had the same boundaries in 6 chlorotic individuals that it had in 4 non-chlorotic women, and that these boundaries, furthermore, agreed with those which had previously been found in healthy males." Although Meinert[148] raised the objection that gastrodiaphany yielded uncertain and deceptive results, Martius[145] was successful in showing that such was not the case. In other instances, Martius and Meltzing employed the method of Meinert (inflation of the stomach with 6 gm. = 90 gr. of tartaric acid, and 8 gm. = 120 gr. of sodium bicarbonate), and in no case of chlorosis could they obtain that visible outline of the lesser curvature which Meinert correctly emphasized as an important sign of gastroptosis. Leo and Brüggemann found a downward displacement of the greater curvature after marked dilatation of the stomach, but usually failed to observe a corresponding descent of the lesser curvature; they consequently do not recognize gastroptosis as a regular concomitant of chlorosis. We can add some observations of our own, which may not be without interest, since we have paid attention to this question since Meinert's first publications. Within three years we have been able to examine carefully for gastroptosis only 6 chlorotics, who had never worn corsets and whose chests and abdomens showed no evidence of constricting clothing. In none of these cases was gastroptosis present (method: marked dilatation with carbonic acid gas); in 5 instances the greater curvature was above the umbilicus, in 1 case it was 1 cm. below, and the lesser curvature was never visible. Judging from the origin, symptoms, and clinical course, these were cases of true chlorosis; the ages of the patients ranged between fifteen and seventeen years. Of these individuals 2 were factory girls, the other 4 belonged to the educated classes. We have also examined a number of chlorotics who were accustomed to wear more or less tight corsets. In these cases we have sometimes seen a considerable descent of the greater curvature and the simultaneous appearance of the outline of the lesser curvature; in other cases this was not observed. We are unable to quote figures in reference to this point, since less stress was laid upon the records of these cases.

As matters stand at the present time, Meinert's teaching—that gastroptosis is to be observed in all cases of chlorosis—can not be maintained. We fully recognize the correctness of Meinert's observations, but we also require him to admit that he is not the only one to decide whether gastroptosis is present or absent, and that he should consider the negative results of other expert observers as well as his own positive ones. Earnest investigators who have made a profound study of the pathology of the digestive organs certainly can not be reproached with the fact that they are unable to recognize a gastroptosis. Small degrees are always difficult to establish, but marked degrees of gastroptosis, such as Meinert found in his patients, give a characteristic picture to the expert which excludes all errors—it matters not whether this or that deviation from the ordinary methods of examination has been employed. The cause of the contradiction may be found, first of all, in differences in the material coming under observation. It would seem that early tight-lacing is the rule in Meinert's vicinity, and if this is true it is natural that he would very frequently observe changes in the position of the abdominal organs. In this case, however, all the more caution should be observed in reaching a conclusion. Meinert makes one statement, of the greatest importance, which he does not seem sufficiently to have considered. He says that of 400 women over thirty years of age with gastroptosis, only one-half had been chlorotic. Meinert helps himself over this fact by the additional hypothesis that gastroptosis alone does not produce chlorosis, but that there must be, in addition, a pathologic irritation of the sympathetic nerves ("gastroptic crises"). Others, who think more cautiously than the creator of the new theory, would be more likely to look upon this ratio as a warning against the causal combination of the two diseases. In the writer's opinion a final decision can be made only in those countries where artificial change of the position of the stomach is more rare. Meinert correctly appreciates the value of such proof, and quotes opinions from foreign countries in which the bad habit of lacing does not exist and in which chlorosis is said to be rare. Such evidence without a profound study of all the conditions of life is, however, without value. In the meantime, the observation of the conditions existing in our own country is of more importance. For some time past there has been a strong feeling against young girls wearing constricting corsets. There are already numerous educated women who devote a great deal of attention to the proper clothing of their daughters, and who provide them with soft yielding corsets, which are supported from the shoulders, and which fulfill their purpose of holding up the breasts without constricting the

abdomen. This movement will spread, and it is to be hoped that the social influence of these women will accomplish more than have the warnings of physicians for a number of centuries. In our own circle of activity we have very often encountered this reform in reference to the clothing of young girls, and yet we found that many of these sensibly clothed individuals had not escaped chlorosis.

From the publications upon the subject and from our personal experience, we would conclude that changes in position of the abdominal organs, particularly of the stomach, are just as frequent among the chlorotics as they are among the other women who are injudiciously dressed; that sometimes even quite marked degrees of artificial deformities may be observed, but that a genetic connection between the changed positions of the organs and chlorosis is very unlikely.

GASTRIC ATONY—GASTRIC DILATATION.

The surprising results of Meinert have also been subjected to another interpretation. Leo,[146] who has studied this question most profoundly, admits that a downward or transverse position of the stomach is encountered in girls who have laced, and also confirms the frequent downward displacement of the lower gastric border (after dilatation, reaching just below the navel, or at most about $\frac{3}{4}$ finger-breadths lower). He, however, considers the actual cause of this displacement to be a pathologic yielding and extensibility of the gastric wall, a condition which we can designate as atony. Such a conception was first held by Pentzoldt,[149] who traced the gastric disturbances of chlorotics to a supposed dilatation of the stomach. Since the difference between gastric atony and gastric dilatation is only one of degree, we will consider them both together.

The frequent occurrence of gastric relaxation is most sharply emphasized by French authors. C. Bouchard[150] states that he has found a more or less pronounced dilatation of the stomach in 80 per cent. of all cases of chlorosis. Couturier,[151] one of Bouchard's pupils, expresses himself in a similar manner; he thinks that chlorosis may arise in consequence of a dilatation of the stomach, and that, on the other hand, chlorosis can itself be the cause of gastric dilatation.

Hayem[152] demonstrated gastric dilatation 27 times in 37 patients. In 24 cases the dilatation was slight; in 3 instances it was extreme. Symons Eccles[153] scarcely ever missed it in chlorotic individuals. Among the German authors, Neusser[154] and A. Pick[155] profess the same opinion.

Unfortunately, all publications do not give convincing evidence of

the correctness of the diagnosis of gastric dilatation. The objection to the publications of Bouchard and of Hayem is that they laid altogether too much weight upon the presence of succussion splashes in the stomach. It is only in rare instances that these are sufficient to verify the diagnosis. Somewhat more confidence may be placed in the results obtained by inflation of the stomach. An unusually marked degree of dilatability, such as those found by Meinert and Leo, at least demonstrates a lessened resistance of the gastric walls to pressure from within, and justifies, to a certain extent, the diagnosis of atony. Even here we are exposed to many sources of error, since the size and shape of the stomach are subject to individual variations. The inflation method does not prevent the confusion of mild degrees of atony with mild degrees of gastroptosis. It is, furthermore, to be considered that a stomach can be abnormally distended by the development of carbonic acid gas and, nevertheless, be able to meet all the natural demands which are made upon its motor power by the ingestion of food. For the clinical decision as to whether gastric atony and dilatation with motor insufficiency are present or not, the results of the inflation method are to be employed only with caution. This question can be decided only by determining whether or not the stomach empties itself of its contents within a time which is to be considered as normal. This normal period, as is well known, varies according to the nature and amount of the food ingested, but by observing the same experimental conditions a constant standard is obtained. If criteria such as these were employed, the number of diagnoses of gastric atony in chlorosis would be materially reduced. Riegel, who has studied the gastric disturbances in chlorotics more profoundly than other German authors, had his assistant, K. Osswald,[132] write: "The motor power of the stomach was always very good; in many cases it was necessary to remove the gastric contents within four hours after the ingestion of the test-meal, since the stomach was entirely empty after five hours." I. A. Hoffman[156] says: "The French report very considerable digestive disturbances, and even state that gastric dilatation is common in chlorotics; in our country I have never seen a true gastric dilatation in chlorosis." From the author's observations, which, similarly to those of Riegel, were based upon the determination of the period of digestion, he is forced to take an intermediate position. In the course of the last ten years he has washed out the stomachs of more than 100 chlorotics, sometimes after a test-breakfast, and sometimes after a hearty meal of meat. In but 11 patients did the stomach retain the food longer than normal; in the great majority of the cases the stomach emptied itself

just as quickly or even more quickly than in healthy individuals. In 6 of the 11 cases just referred to, the anamneses stated that the individuals had had gastric disturbances since their early childhood.

When the differences of opinion are so great about what is a comparatively simple question, the explanation of these differences must be sought in different conceptions of the terms "gastric atony, gastric dilatation," and in differences in the methods of examination. The diagnoses of the French authors rest for the most part upon the nature of the succussion splash; we agree with their statements that this sound may be obtained more easily and for a longer period after meals in chlorotics than in healthy women with rigid abdominal walls, but we do not agree with them in their interpretation of this phenomenon. The succussion splash is hard to obtain in healthy individuals with rigid abdominal walls unless nothing but liquids has just been ingested. If the sound is readily obtained after a solid or a semisolid meal, there are several possibilities:

1. Downward displacement of the stomach—frequently present in chlorotics, as in other young girls who wear tight corsets.

2. Abnormal relaxation of the gastric walls, so that they do not contract so firmly about the gastric contents; they evade the percussing stroke and allow of a more marked agitation of the gastric contents. This is frequently the cause for the readiness with which the succussion splash may be obtained in chlorosis.

3. Abnormal liquefaction of the contents, whereby the bubbling of the fluid is more easily produced by percussion of the abdominal wall. Those who have washed out many chlorotic stomachs will be able to confirm the statement that the gastric contents are frequently of an almost watery consistence. If the stomach is washed out a half-hour after the test-breakfast, more fluid is frequently obtained than would correspond to the volume of the test-meal. At the same time the gastric juice gives a very marked reaction for hydrochloric acid. The significance of this is clear—the secretion not only contains an excess of acid, but it is also increased in amount (supersecretion). If we depend upon the results of palpation in these cases, which, in the author's opinion, are not so very infrequent, we are very likely to regard them as instances of atony or even of dilatation.

He considers it necessary to emphasize the fact that the motor function of the stomach is well maintained in most cases of chlorosis, for this point has a most important bearing upon the treatment. For a stomach with motor insufficiency quite a different line of dietetic measures is to be carried out than would be observed in the treatment of a

stomach with a normal capacity for work. He has frequently had an opportunity to observe how much the teaching of gastric dilatation in chlorosis has influenced the therapeutics of the physician. He has seen several young French girls who, on account of a supposed gastric dilatation, had been placed upon a very rigid diet by their Parisian physicians; as a result the chlorosis was combined with a marked degree of emaciation. In none of these cases could he be convinced of the existence of a true dilatation, or motor insufficiency, and had the satisfaction of seeing the young women rapidly recover when placed upon an abundant diet.

THE SECRETION OF HYDROCHLORIC ACID.

Manassein [157] found a decreased production of hydrochloric acid in the stomachs of anemic animals (after venesection). It is characteristic of a certain trend in medicine that the results of this investigation upon animals have been introduced into human pathology without further criticism. Upon it was based a new treatment—the administration of hydrochloric acid (Zander [14]). The author can still remember, from his student days, how the clinical teacher would refer to the experiments of Manassein, and discuss the question as to whether chlorotics should be given iron at once, or whether it was not better to precede the administration of iron with large doses of hydrochloric acid. Even at the present time there is a periodic revival of the praises of hydrochloric acid and of its unconditional administration in chlorosis (O. Rosenbach,[158] Edlefsen,[159] K. Mordhorst [160]). The old experiments of Manassein are always referred to—an unusual glorification of animal experimentation and a still more unusual misconception of clinical facts. The teaching of a lack of hydrochloric acid has also played an important rôle in the theories of the origin of chlorosis. The much-quoted and highly valued hypotheses of Bunge,[161] which are sometimes regarded as dogmas, are based upon such an assumption.

Riegel [162] was the first to disregard experiments upon animals in this connection, and to carry out clinical investigations in chlorotic individuals. In his first report he referred to 3 cases, in all of which the gastric contents gave a marked reaction for free hydrochloric acid; the acidity varied in the first case between 0.22 and 0.26 per cent., in the second case between 0.23 and 0.30 per cent., and in the third case between 0.38 and 0.46 per cent. These increased amounts are striking. Two works appeared later, from Riegel's clinic, which supported his first publications by showing that marked and even maximum degrees of acidity (due to a marked excess of free hydrochloric acid) are not

the exception, but the rule (Grüne,[163] Osswald[132]). Grüne reported 19, and Osswald 21 cases. In some instances there was as much as 0.58 per cent. of hydrochloric acid present. The authors never encountered pathologic diminutions of production of hydrochloric acid, not even in cases which were associated with pronounced dyspeptic symptoms.

Other investigators have tried to solve this question, not always with the same result. Leube's clinic furnished a report of 30 cases of chlorosis (Schätzel[164]): hydrochloric acid was diminished in 2, normal in 6, and increased in 22. This publication, practically agreeing with the teaching of Riegel, is the more worthy of note, since an earlier article from the same clinic (Ritter and Hirsch[165]), based upon only 2 cases, had expressed an opposite opinion. The author had Rethers[133] publish a small series of statistics. Of 20 cases of pure chlorosis, 8 had acidities above normal (0.29–0.38 per cent.), with marked reactions for free hydrochloric acid, in 7 cases the acidities varied within normal limits (0.12–0.28 per cent.), and in 5 instances free hydrochloric acid was not found, in spite of frequent examination; in the meantime 10 more cases came under observation, 8 with hyperacidity, 2 with normal reactions. In 72 cases, Hayem[166] found the amount of hydrochloric acid increased in 42, diminished in 28, and normal in 2. Cantu,[167] like Riegel, states that the over-production of hydrochloric acid is characteristic of chlorosis; this symptom is said to be absent only when the disease is of very long duration. Rosenheim,[137] Buzdygan and Gluzinski,[168] Maurer,[169] and Schroth[170] found, on the whole, normal acidities with slight and rare deviations. The only authors who frequently found a diminution of hydrochloric acid are Lenhartz[171] and Neusser.[154] The article by Neusser contains no exact statistics.

If we review the entire subject, we become convinced that a lack of hydrochloric acid can no longer be regarded as a constant concomitant of chlorosis and, furthermore, that none of the theories are justified which are based upon this supposed lack of hydrochloric acid. The hydrochloric acid is very frequently increased in chlorotic stomachs; acidities seen in no other disease have sometimes been observed. On the other hand, investigations show that the hyperacidity, which was so regularly observed in the patients of the clinic at Giessen, is not a necessary attribute of chlorosis. It is evident that all sorts of auxiliary influences are at work. The author has tried to decide from his own observations and the clinical histories of others—when they have been given in detail—whether the grade of the anemia, the age of the patient, or other factors exerted any influence, and whether the acidity of the gastric juice corresponded to definite disturbances of digestion. He

has, however, been unable to discover any regular relation. A more exact detailed comparative observation of patients would, nevertheless, enable one to discover why the normal or increased production of hydrochloric acid in most cases gives way to a diminished secretion in others. There are no explanations for the hyperacidity that are free from objection. We might think of the increased amount of chlorin in the blood, which, according to the investigations of W. v. Moraczewski,[172] is said to be indicative of chlorosis. It is not improbably dependent upon the nervous system. The gastric mucous membrane is hyperesthetic (Th. Rosenheim[187]); this fact not only explains the numerous subjective disturbances, but it is also the cause of a more marked stimulus to the secretory centers, resulting in the production of an abnormally acid, and frequently an abnormally abundant, gastric juice (see pages 410 and 416).

DEFECATION—DECOMPOSITION IN THE INTESTINE.

The author would not return to the condition of the bowels in chlorosis if it were not associated with an important practical and theoretical question. The older writers mentioned sluggishness of the bowels only as a concomitant symptom of chlorosis, basing it upon the weakness of the anemic intestine, the weakness of the abdominal muscles, and the deficient intestinal secretion. Duclos,[20] Sir Andrew Clark,[19] Ch. Bouchard,[150] Nothnagel,[21] and others subsequently regarded constipation as a causal factor in the production of chlorosis. The train of thought was as follows: Fecal stasis results in the establishment of abnormal processes of decomposition within the intestinal tract, particularly to increased putrefaction of the albumins; poisonous substances are formed which are absorbed into the circulation and destroy the hemoglobin or damage the blood-building organs.

Bunge[161] has a different idea in reference to the increased decomposition of the albumins; he places the most importance upon the origin of large quantities of sulphuretted hydrogen from the putrefying albumins, and its stable combination with the iron in the intestinal tract. Bunge[1] has since withdrawn this hypothesis as untenable, but it is mentioned here in order to show the prevalence of the teaching of the increased decomposition of the albumins. Sir Andrew Clark[19] regards the changed mode of life of young girls at the time of puberty as the cause of constipation. He refers to deficient exercise, the use of the corset, the insufficient ingestion of food on account of the fear of obesity, and states that in girls of this age the sense of shame is so finely developed that they dread being seen in the vicinity of the closet and consequently repair to this locality as infrequently as possible. In this

manner habitual constipation is produced. Hüllman[173] lays more stress upon the development of the pelvic organs; he believes that the growth and maturation of the sexual organs exercises pressure upon the rectum and interferes with its evacuation. These and similar conceptions have naturally given rise to corresponding therapeutic measures; the regulation of the bowels being particularly insisted upon by Duclos, Clark, Hüllman, Nothnagel, and others. The question is consequently one of preëminent practical interest. It is to be solved partly by clinical observation and partly by a chemic investigation of the excretions.

From a clinical standpoint it must be recognized that many chlorotics suffer from marked constipation; in order to utilize this for the pathogenesis of chlorosis we must have statistics which allow of a comparison between the condition of the bowels in chlorotic and in non-chlorotic girls and women. Such a series of statistics has never been published and it would be very difficult to obtain exact and convincing statements. The author, as already stated, has been unable to observe any difference in this respect between chlorotic and non-chlorotic women. In his present practice the disease seems to be more frequently accompanied by sluggishness of the bowels than was the case in his earlier experience. Constipation was observed in 60 per cent. of the cases; only once was the constipation actually severe and difficult to overcome, in the other instances there were only slight irregularities, which occurred periodically and which—when not combated—delayed the movements for one or two days. It should also be added that in this locality constipation seems to be more common not only in chlorotics, but also in other young girls.

The following statistics of 182 cases of chlorosis were obtained during the author's association with the clinic at Giessen and with the Second Medical Clinic of Berlin:

Regular daily evacuations without laxatives,	in	101	patients	=	55.5	per cent.
Evacuations at an average interval of one, or of one and one-half days	"	5	"	=	2.7	"
Evacuations at an average interval of one and one-half or of two days	"	14	"	=	7.7	"
Evacuations at an average interval of two or three days	"	40	"	=	21.9	"
Evacuations at an average interval of three or four days	"	9	"	=	4.9	"
Tendency to diarrhea	"	9	"	=	4.9	"
Alternate diarrhea and constipation	"	4	"	=	2.2	"

In accord with the experience of most physicians these figures show conclusively that constipation is a frequent, but by no means regular, concomitant of chlorosis. There is no reason for designating it as a cause of the disease.

Much more important than the frequent absence of constipation in chlorosis is the fact that we often encounter mild, moderate and severe degrees of habitual constipation in every-day practice, without the slightest symptoms of chlorosis and with quite different sequelæ than would correspond to this disease. Dogmatic prejudice alone could be blind to the conclusive proof of this fact.

Although we have stated that constipation is not a regular concomitant of chlorosis and that the sequelæ of constipation do not resemble the disease, we have not yet touched upon the essential point of the discussion. It must be determined whether abnormal processes of decomposition occur in the intestinal tract with the formation of poisons so that we would have to consider intestinal auto-intoxication as the cause of chlorosis. To make the solution of this question dependent upon a more or less marked degree of inactivity of the lower bowel, is evidence of a superficial method of observation. The most severe enterogenic intoxications known, such as cholera, for example, are associated with profuse evacuations; the presence of intestinal parasites gives rise to severe toxic anemia, entirely independent of the presence or absence of constipation (bothriocephalus anemia); in other metabolic diseases, the origin of which is doubtless to be sought in abnormal decomposition of the intestinal contents (diaminuria, alkaptonuria), the condition of the bowels is of subordinate importance. We must, consequently, look about for other criteria and, above all, try to discover whether such abnormal products of decomposition are to be found. The work of Th. Rethers [132] marks the first advance in this direction. Since there were but few reports upon the amount of indican in the urine of chlorotic individuals (Hennige,[174] Heinemann,[175] Senator,[176] Ortweiler [177])—the indigo reaction being feeble with rare exceptions—the author had Rethers determine the total quantity of the conjugate sulphates in the urine, since these combinations (indol, skatol, phenol-sulphate) form a good indication of the extent of the putrefactive decomposition of the albumins in the intestines.

The investigations were made upon 18 cases of chlorosis, which were almost, without exception, instances of severe types. The quality and quantity of the diet was approximately the same in all these instances (much albumin, little carbohydrates and milk). In healthy individuals, mostly women who were on the same diet, the author had usually found the daily amount of the conjugate sulphates to vary from 0.12–0.25 gm., sometimes more, sometimes less. Of these 18 chlorotics

3 secreted over 0.30	gm.	1 secreted over 0.20–0.25	gm.
5 " " 0.25–0.30	"	9 " less than 0.20	"

These were the average amounts obtained from repeated daily examinations of the urine.

Rethers concluded from this that gastro-intestinal disturbances producing an increased putrefaction of the albumins are not rare in chlorosis, but that they are not frequent enough to be made responsible for the origin of the disease.

After the appearance of Rether's dissertation, the author carried out parallel experiments upon 4 chlorotic and 4 healthy girls. The diet was exactly the same as in the investigations of Rethers. The urines were examined for three days, and the following average daily amounts of conjugate sulphates were found in the urines of the chlorotics—0.17, 0.19, 0.25, 0.26 gm.; the urines of the healthy girls contained 0.165, 0.21, 0,24, 0.28 gm.

As Albu[173] rightly remarks, the last word upon this subject has not been said; in the meantime, proof being offered only that the form of albuminous decomposition which terminates in the formation of aromatic substances can not be of decisive importance for the origin of chlorosis, the ptomains and poisonous albuminous bodies would still have to be considered. The hypotheses of Forchheimer[22] consider these substances, but it is quite useless to pursue the subject further until the realm of positive knowledge has been considerably enlarged.

THE ABSORPTION OF FOOD.

Investigations of the absorption of nutritive material give an idea of the entire amount of work done by the gastro-intestinal tract; they have not been carried out in large numbers of chlorotics. We will place the results of those known up to the present time in a small table:

Author.	Duration of the experiment.	Nutrition per day. Total solids in gm.	Nitrogen in gm.	Fat in gm.	Loss in feces per day. Total solids in gm.	Nitrogen in gm.	Fat in gm.
Wallerstein[113]	6 days	347	16.46	39.26	16.3	1.16	4.96
Lipmann-Wulf[75] and v. Noorden.	7 "	441	12.88	85.86	22.4	0.97	4.22
	7 "	488	13.06	98.47	23.5	0.84	4.97
	5 "	483	12.78	93.65	24.2	1.17	5.10

All these were severe cases of chlorosis. The results showed a normal absorption of total solids, of the nitrogen, and of the fat. The only striking feature is the poor absorption of the fats in Wallerstein's patient; 12.63 per cent. of the fats ingested (or of the substances soluble in ether) passed out with the feces. This high percentage should not be surprising, nor should it be designated as pathologic, since the diet contains very little fat, and, as is well known, the pro-

portion absorbed under such conditions is always quite small (v. Noorden[179]).

Further investigations are still to be desired. In rare cases the feces of chlorotics resemble the clay-colored stools of icterus (v. Jaksch,[180] Nothnagel,[181]); this condition always seems to be transitory in its character. We have encountered these clay-colored stools only twice in chlorosis, although we have made inquiries upon this point in every case for the last eight years. This patient was fed upon ordinary mixed hospital diet; the feces were of a grayish-clay color, and the dried residue contained 31.2 per cent. of fat, not an excessive quantity. The patient was, unfortunately, so unreliable that no accurate experiments could be carried out; in a few days the bowel movements lost the gray color and did not regain it throughout the entire period of observation. In future cases we must particularly observe whether this gray color is due to the large amount of fat or to the decreased amount of bile. In accord with Nothnagel, we were able to determine in our case that there was certainly not a complete absence of the derivatives of the biliary coloring-matters. A decrease of hydrobilirubin is not rare; we shall have to treat of this more in detail upon a subsequent occasion.

[Vannini[1] has studied the metabolism in chlorosis and refers to previous investigations along the same line. He found a distinct nitrogen retention. The absorption from the intestines of proteids, fats, and carbohydrates was normal. The water balance varies widely in different cases and at different times. The conditions of the urine are generally normal as to the quantity, specific gravity, and acidity. The nitrogenous elements vary greatly, especially the ammonia and urea. The ethereal sulphates are generally not increased, but there is not infrequently some increase in the neutral sulphur. Earthy phosphates are often diminished. The calcium, magnesium, sodium, and potassium balance is normal.—Ed.]

THE SPLEEN.

According to the statements of the older authors, the spleen of chlorotics shows no changes; it is particularly stated that it is not enlarged. Immermann,[182] for example, states that "the two cases of Führer[183] and Scharlau[184] which came to autopsy and in which the spleens were enlarged, soft, and pigmented, were very exceptional." In some other autopsy reports which the author consulted no mention is made of enlargement of the spleen. Exceptions are found in those

[1] *Virchow's Archiv*, clxviii., 1904, p. 375.

cases where complications existed that usually give rise to splenic enlargements, such as pyemia, for example. Among others in this class is the case of Mildner [132] with a severe bed-sore and infectious venous thrombosis, and the case of Le Sage [132] with sinus thrombosis and purulent peri-oöphoritis. In recent years, on the contrary, clinicians have frequently pointed out the occurrence of splenic enlargements in extreme cases of chlorosis. Jacobi [48] found this symptom in 5 out of 7 cases, and regards it as a regular symptom of the severe type. Chvostek [185] reports enlargement of the spleen 21 times in 56 cases; the anterior pole of the spleen was palpable 13 times; in 8 cases the enlargement was demonstrable by percussion only. In the majority of these cases all other causes of splenic swelling were excluded. Chvostek believes that active regenerative processes occur in the blood of chlorotics, and to this he attributes the enlargement of the spleen. Rummo and Dori [186] frequently found a splenic enlargement when they treated chlorotic individuals with subcutaneous injections of citrate of iron and ammonium. The splenic enlargement appeared when the chlorosis improved and while the blood was in process of active regeneration. In Jacobi's cases the opposite condition obtained—the splenic enlargement disappeared with the cure of the chlorosis. Apparently unacquainted with the works of his predecessors, Clément [28] writes of the frequent enlargement of the spleen in chlorosis. A new author, a new explanation! Clément regards the splenic swelling as proof of the infectious nature of chlorosis.

In the records of the Clinic at Giessen and of the Second Medical Clinic of Berlin, we find statements in reference to the condition of the spleen in 168 cases of chlorosis:

Spleen not palpable, dulness less than 7 cm.	in 122	cases	= 72.6 per cent.
" " " " more " 7 "	" 21	"	= 12.5 "
" enlarged, demonstrable by palpation	" 15	"	= 8.9 "
" " without more exact statement	" 10	"	= 6.0 "

In the chlorotics examined in our office or in consultation during the last two years, and in whom the anemia was almost, without exception, of a most marked degree, the spleen was much more frequently palpable than was the case in the hospital statistics. In 45 per cent. of the cases it projected beyond the costal margin during inspiration.

It may be doubted whether there is really a corresponding enlargement of the spleen every time the splenic dulness is increased and the apex of the spleen is palpable. We frequently have to do with girls and women in whom the position of the abdominal organs has been changed by inappropriate clothing. The spleen is particularly likely

to be involved in such displacements, and in many instances it may be rather a wandering or dislocated spleen than an enlargement of the organ.

These objections can be made only to a certain number of observations. In many instances a true enlargement of the spleen can not be denied. From my own experience the splenic swelling seems to accompany only the severe forms of chlorotic anemia and to disappear rapidly during recovery.

These remarks may cause more attention to be given to the condition of the spleen in chlorosis. In view of the paucity of details, it is not worth while to consider the significance of the splenic enlargement at the present time.

THE SEXUAL ORGANS.

We have previously repeatedly emphasized the fact that intimate relations between the genital apparatus and the disturbances of blood-formation leading to chlorosis are not to be denied. According to our supposition the explanation is to be found in anomalies of metabolism in some portion of the sexual apparatus (see pages 348 and 351).

At this place we will consider only those phenomena which are capable of objective demonstration. The anatomic and menstrual anomalies are to be particularly discussed.

DISTURBANCES OF DEVELOPMENT.

The pathologic anatomists, led by Rokitansky[97] and Virchow,[1] taught that a deficient development of the genitalia was found in individuals who had suffered from severe and incurable forms of chlorosis. The autopsy reports upon which this teaching is based speak mostly of smallness of the uterus (uterus infantilis) and of small ovaries with a greatly decreased number of follicles. It would be most praiseworthy if the pathologic anatomist and clinician would work together to furnish a larger series of statistics upon these cases. The author has looked over nearly all of the published postmortem records of cases of chlororosis and the result was not worth the trouble. In but 27 cases were there statements in reference to the anatomy of the sexual organs; in 25 instances the descriptions were such that the presence of developmental disturbances of the uterus or of the ovaries could be assumed with some degree of certainty. It would be much better than this variety of statistics if we would start with those cases which present evidence of retarded development at autopsy and then to determine whether these individuals had ever had chlorosis.

In view of the scarcity of pathologic material we are particularly

indebted to H. Stieda,[9] who undertook to solve this question by means of gynecologic examinations upon the living.

In the gynecologic "Poliklinik" at Freiburg, Stieda attempted to determine whether those conditions which must be designated as retarded development or developmental disturbances (the so-called "signs of degeneration") of the body, particularly of the pelvis, breasts, and genitalia, were more frequent in chlorotics than in other persons.

The examinations were made in 23 chlorotics. In 14 cases (61 per cent.) the pelvis resembled that of a puerile type (lessened transverse measurement of the anterior half of the pelvic ring).

In 9 cases (39.1 per cent.) there was a deficient development of the external genitalia (labia majora and minora, clitoris, pubic hair).

No anomalies of the hymen or vagina were found.

In 5 cases there was an infantile uterus; in 1 instance, a uterus duplex.

In 12 cases the ovaries were smaller than normal; in 9 cases the difference was slight, in 3 instances it was very considerable.

In 5 cases the breasts were poorly developed; in 7 cases only moderately so, making a total of 52.2 per cent.

These degenerative signs occurred sometimes alone and sometimes in groups. Taken altogether, no less than 73.9 per cent. of the chlorotic persons examined exhibited one or more of these developmental anomalies.

During the same period of observation, non-chlorotic patients were examined for the purpose of comparison.

Among 233 persons, the above-mentioned anomalies, either alone or in association with each other, were found in 64 individuals—*i. e.*, in 27.5 per cent.

The details of these anomalies are as follows:

Pelvic anomalies in 23.6 per cent. (puerile pelvis in 9.9 per cent.).

Deficient development of the external genitalia in 4.7 per cent., of uterus in 4.3 per cent., and of the ovaries in 0.9 per cent.

Deficient development of the breasts in 3.9 per cent.

In a previous collection of cases from the same clinic Wiedow[187] had found that one or more of the so-called degenerative signs were found in 20 per cent. of the patients.

Although the number of cases examined by Stieda is small, the author does not think we should hesitate to promulgate Stieda's results, together with the comparative percentages, since they practically constitute the only serviceable collection of material that we posssess at the present time. The final conclusion is important and surprising:

73.9 per cent. of the chlorotic, and only 20–27.5 per cent. of the non-chlorotic individuals exhibited one or more developmental anomalies.

The significance of the result is such that we are inclined to await the publication of a larger series of observations. Stieda, like Immermann,[1] is inclined to believe that chlorosis is independent of arrested development; these authors both look upon the arrested development of the genitalia, on the one hand, and the deficient formation of blood, upon the other, as coördinated "degenerative signs" or disturbances of development. This certainly must be admitted as far as a large number of the anomalies are concerned—for example, where the arrested development is limited to the pelvic bones or to the external genitalia. In the decision of the question as to whether the deficient maturation of the uterus, and particularly of the ovaries, exerts any deleterious influence upon the activity of the hematopoietic organs, these clinical reports are of no more aid to us than the previously published autopsy records.

MENSTRUATION.

We are not justified in drawing any far-reaching conclusions from the condition of the menses. Nevertheless, it is worthy of note that, of all diseases, chlorosis is most frequently accompanied by menstrual disturbances. This is also suggestive of the intimate relations which exist between the processes occurring in the genitalia and those taking place in the hematopoietic organs.

Various possible interpretations of the nature of this connection have been stated. We will limit ourselves to briefly outlining some of them:

1. Chlorosis is a result of the menstrual disturbances. Some writers would trace chlorosis directly to the losses of menstrual blood. Such a hypothesis as this disregards the facts that many girls are attacked by chlorosis before they have ever menstruated, and that in a still larger number, who become chlorotic later, the losses of blood are much too small and much too infrequent to produce a severe anemia. In view of the previous histories of some attacks of chlorosis and in view of the numerous cases in which the menstruation became scanty or entirely ceased with the appearance of the disease, an etiologic significance can hardly be ascribed to the menstrual bleeding—not even in an individual case when the chlorosis is preceded or accompanied by marked and foul-smelling losses of blood.

The absence of the menses has also been made responsible for chlorosis. Charrin[29] regards the disease as a variety of menstrual intoxica-

tion. According to his conception, when the menses are scanty, toxins which are injurious to the blood and to blood-formation are retained in the body. This is practically equivalent to one of the widespread beliefs of the laity.

2. The menstrual disturbances are the results of chlorosis. The champions of this theory trace both the diminution and infrequency of the menstrual flow, as well as greater frequency, menorrhagia, and pains of the most varied descriptions, to the basal disease. It is such a varied conglomeration that we might say there is almost no form of menstrual anomaly which has not been explained by the impoverishment of the blood.

It seems most natural to attribute a scantiness of the menses, or even amenorrhea, to the chlorotic quality of the blood. Experience favors this view, since the menses frequently become more profuse and more regular with improvement of the anemia. Objections are encountered, however, when we draw comparisons with other forms of anemia. So-called pernicious anemia, leukemia, and many marked cases of secondary anemia, are more prone to produce an exaggeration than a diminution of the menstrual flow. At all events, the disturbances of menstruation in chlorosis are too manifold and too independent of the severity of the disease to be considered as uniform and intimate consequences of the affection.

3. The anemia and the menstrual anomalies do not hold any causal relations with each other, but they are both dependent upon other common causes. This is a natural elaboration of our previously stated hypothesis of the origin of chlorosis (see pages 347 and 355) and we incline to this view. We have assumed that the attack of chlorosis is excited by pathologic-metabolic processes in the genitalia, particularly in the ovaries and probably dependent upon the maturation of the ova, or even by a deterioration of the normal processes of metabolism. Pathologic processes in the ovaries must also be made responsible for the disturbances of menstruation. Since the processes within the ovaries which lead to impairment of blood-formation and to anomalies of the menstrual flow need not necessarily be identical, the anemia may be associated with the most varied forms and degrees of menstrual disturbances.

We will leave these theories and give a brief survey of the frequency of menstrual disturbances in chlorosis. In addition to some small series of observations of previous authors we can furnish a larger, new, and carefully selected amount of statistic matter.

H. Schulze[188] reports of 26 chlorotics:

5 times, normal menstruation;
4 " no menstruation as yet;
7 " normal menstruation before the disease—when the disease appeared the menstrual flow became scanty in 4, and more profuse in 3 instances;
10 " complete amenorrhea during the chlorosis.

Hayem[1] states that girls who have not yet menstruated, only rarely become chlorotic. The condition of the menses before the disease, as regards both quantity and regularity, does not differ from that observed in girls who do not become chlorotic. With the appearance of the chlorosis there is almost always an impairment of the menstrual process. Of 65 patients, 24 lost their menses with the appearance of the disease, 36 suffered a considerable diminution in the amount of the menstrual flow, 4 showed no change whatever, and 1 lost larger amounts of blood at more frequent intervals.

Ossent[3] encountered disturbances of menstruation 68 times in 195 chlorotics (34.9 per cent.); the periods were sometimes too profuse, sometimes too scanty, painful, irregular, etc.; more exact statements are wanting. In 14 cases the periods had not yet made their appearance (7.2 per cent.); among these were 5 girls over 17 years of age and 9 younger individuals. Altogether menstrual anomalies were present in 42 per cent. of the cases. This percentage is quite considerable, but it is considerably less than that of Hayem.

Stieda[9] informs us that of his 23 chlorotics, only 7 had menstruated regularly; their periods were scanty. One patient, nineteen years of age, had not yet menstruated; in 2 individuals, menstruation had existed for a short time and then ceased entirely. The remainder had menstruated irregularly, 3 of these scantily, and 4 profusely. The patients with profuse bleeding also had endometritis, so that the latter affection was more responsible for the menorrhagia than was the chlorosis. Disregarding these particular cases, the menstrual process, as a rule, seemed to be impaired.

The authors' own statistics are based upon a collection of 215 cases: Of 215 chlorotics, 30 had not yet menstruated at the time of observation (13.9 per cent.). Of these

1 patient was	13 years of age.			1 patient was	18 years of age.		
3 patients were	14 years of age.			4 patients were	19	"	"
6 "	15	"	"	3 "	20	"	"
6 "	16	"	"	1 patient was	21	"	"
3 "	17	"	"	2 patients were	24	"	"

In 26 other cases (12.1 per cent.), the chlorosis had likewise broken out before the first appearance of menstruation; these patients did not come under observation, however, until after the beginning of menstruation, usually during the second or third attack.

Number of cases.	The chlorosis first appeared.	The first menstruation occurred in these cases at
2	before the 12th year.	13 and 15 years of age.
2	in " 12th "	14 " 15 " "
5	" " 14th "	15, 15, 16, 16, 17 years of age.
4	" " 15th "	16, 17, 17, 19 "
4	" " 16th "	17, 17, 18, 18 "
5	" " 17th "	18, 18, 18, 19, 19 "
3	" " 18th "	19, 19, 20 "
1	" " 19th "	"

Of 215 patients, there were consequently 56 (26 per cent.) who had not yet menstruated when the disease began.

In 30 patients (13.9 per cent.), the chlorosis appeared at the same time or immediately after the first menstruation. Of these cases

8	commenced at the	age of	14	years.
13	"	"	15	"
5	"	"	16	"
1	"	"	17	"
1	"	"	18	"
2	"	"	20	"

In 129 patients (60 per cent.), there was a longer period of time between the first menstruation and the beginning of the disease:

Number of cases.	First menstruation.	Number of times menstruation occurred. (Time between first menstruation and the chlorosis is placed over each column.)							
	yr.	1 yr.	2 yr.	3 yr.	4 yr.	5 yr.	6 yr.	7 yr.	over 7 yr.
2	before 12	—	—	—	—	1	1		
5	at 12	—	—	—	2	—	—	1	2
16	" 13	1	—	3	1	3	1	3	4
26	" 14	5	4	4	4	1	4	—	4
29	" 15	11	3	3	4	2	3	2	1
27	" 16	5	8	5	4	2	2	—	1
10	" 17	2	1	2	2	2	1		
8	" 18	3	1	2	1	1			
4	" 19	1	1	1	1				
1	" 20	—	1						
1	" 21	—	—	—	1				
	Total	28	19	20	20	12	12	6	12

It is also interesting to note the number of cases in which the menses had not appeared at the end of the seventeenth year—*i. e.*, the extreme limit of what might still be designated as normal. This was the case in 59 (27.4 per cent.) of the patients; of these 31 had been chlorotic before the first menstruation, 28 had become anemic with the appearance of the menses or shortly afterward.

There are statements in reference to the amount and frequency of the menstruation in 173 of the authors' clinical records.

In 59 patients (34.1 per cent.) the menses were always regular—*i. e.*, before and during the chlorosis.

34 (19.6 per cent.) designated the menstrual amount as moderate.
15 (8.7 ") " " " scanty.
10 (5.8 ") " " " profuse.

In 49 patients (28.3 per cent.) the menses were always irregular—*i. e.*, before and during the chlorosis:

15 (8.7 per cent.) designated the menstrual amount as moderate.
29 (16.3 ") " " periods as scanty, sometimes small in amount, sometimes of too infrequent occurrence.
5 (2.9 per cent.) designated the periods as profuse, sometimes large in amount, sometimes of too frequent occurrence.

In 65 patients (37.5 per cent.) in whom menstruation had been more or less regular, the process changed with the appearance of the chlorosis.

It ceased completely in 44 patients (25.4 per cent.).
It became more scanty or more rare in 17 patients (10 per cent.).
It " profuse " frequent in 4 patients (2.3 per cent.).

Altogether, there was an impairment of the menstrual process, either before or with the appearance of the chlorosis, in 105 patients (60.7 per cent.). To these may be added the 56 chlorotics who had not yet menstruated when the disease first appeared. If we compare this total of 161 with the entire number of chlorotics whose clinical histories mentioned the menstrual condition (215), we learn that 77.2 per cent. of the patients exhibited an impairment of the menstrual process.

As long as amenorrhea exists there is small possibility of conception, but this is not excluded. I have only recently seen 2 cases in which impregnation had occurred after the existence of chlorotic amenorrhea for several months. Chlorosis seems to render impregnation more difficult not only during the amenorrhea, but throughout the entire course of the disease.

LEUKORRHEA.

Of the other pathologic phenomena occurring in the sexual apparatus, and which undoubtedly hold a relation to chlorosis, we must still mention leukorrhea. The non-sanguineous excretions in women are so frequent and have such a varied etiology that it is quite difficult to pick out those cases in which chlorosis can be regarded as the only cause. Of 250 chlorotics, no less than 55 (22 per cent.) had the "whites," either temporarily or throughout the course of the disease.

Many of these cases were undoubtedly complicated by gonorrhea and other diseases of the vagina and uterus. Nevertheless, 18 cases (7.1 per cent.) are worthy of particular attention, since the genitalia were in a virginal condition and exhibited no evidence of improper irritation. As a matter of fact, leukorrhea might be found in a much greater percentage of chlorotics in spite of completely intact genitalia; the relatively low number given above is explained by the fact that these women came from classes of society in which no great weight is placed upon the preservation of virginity.

If we wish to determine the clinical relations of leukorrhea to chlorosis we must consider only those patients who have not yet had sexual intercourse. We then find the following state of affairs:

In a large number of cases there is not a trace of leukorrhea during the entire course of the chlorosis. This is true of both mild and severe forms of the disease.

In many patients every menstruation is succeeeded by a yellowish-white creamy discharge, which lasts longer than did the menstrual flow; this is particularly observed in chlorotics who tend to have very scanty menses. The leukorrhea is most marked two or three days after the cessation of menstruation. The discharge has no irritating qualities and it is only when the patients are particularly uncleanly that the external genitalia become inflamed.

Many patients have the discharge for weeks and months. Most patients suffer with complete amenorrhea as long as the leukorrhea is present. Chlorotics who normally menstruate rarely have a permanent leukorrhea between the catamenia. The pathologic secretion varies greatly in amount; the discharge is often very profuse and the cause of great discomfort. Inflammation of the external genitalia is much more frequent in these cases than in the instances of postmenstrual leukorrhea above described. Women and girls not rarely suffer from marked sexual excitement as long as this form of leukorrhea is present.

It is evident that both the postmenstrual and the continuous forms of leukorrhea are dependent upon chlorosis; they do not seem to be due to inflammation, but simply represent an intensification of the normal secretory process. In many cases the intensity of the leukorrhea maintains a parallel with the general condition of the patient; this has given rise to the popular belief that "leukorrhea weakens the body." Many mothers regard this symptom as the origin and nucleus of the entire disease, and take their daughters to gynecologists. Unfortunately, it repeatedly happens that the specialist institutes gynecologic treatment for the simple leukorrhea. Experienced gynecologists condemn such a

practice as strongly as do the representative medical practitioners. The best, surest, and only admissible treatment of this form of leukorrhea is the dietetic, hygienic, and medical treatment of the chlorosis.

THE ORGANS OF SPECIAL SENSE.

THE EAR.

The milder subjective symptoms, such as tinnitus aurium, will not be discussed under this heading, since they have already been mentioned in the description of the general symptomatology. The disturbances are usually so slight that they are disregarded; many patients fail to recall them until questioned upon this point. Nevertheless, there are exceptional cases in which the tinnitus and other auditory sensations, or even auditory hallucinations, are present to an extremely disagreeable degree and greatly annoy the patient, both by their severity and by their obstinacy. In these cases it is impossible to find any impairment of hearing or any pathologic change in the external or internal ear. Such phenomena are simply manifestations of disturbances occurring exclusively in the nervous apparatus. It has been attempted to make the marked and continuous ringing in the ears dependent upon the murmurs which are objectively perceptible in the internal jugular vein or in the cerebral sinuses. This is, however, out of the question. The author has frequently heard loud murmurs over the mastoid process and the region just above it, when there were absolutely no complaints of subjective auditory symptoms; and, vice versa, these objective murmurs were only slightly marked in patients who had pronounced pathologic auditory phenomena. The two conditions were found together in isolated cases only.

At this place, we will refer to a rare case, in the course of which the power of auditory perception was completely lost for hours. The first time this condition was observed it immediately succeeded an attack of unconsciousness; when the patient came to, all the sensations and functions returned to the normal, with the exception of hearing, which was absent for ten hours. The condition repeatedly returned without a preceding attack of unconsciousness.

A certain parallel usually exists between the severity of the disease in general and the subjective auditory phenomena; at least, it may be readily perceived in individual cases. These disturbances completely disappear with the cure of the chlorosis. Permanent detrimental results are never observed.

THE EYE.

Ophthalmic symptoms are very common in chlorosis.[189] A temporary flickering before the eyes and blackness of vision is complained of in nearly every case of a severe type. Ocular pains, either spontaneous or following eye-strain, are likwise rarely absent. The one or the other symptom may be the more marked, and the oculist is the first to discover that the patient is suffering from chlorosis. The phenomena of the so-called blackness of vision, if they are well-pronounced in an individual case, are particularly important and alarming to the patient. The attacks follow a fainting fit or paroxysms of fainting, or they may appear spontaneously. Ordinarily the attack is of but short duration, a half minute or several minutes; in other instances it may last for hours.

Not long since the following rare case occurred in the authors' practice.

The patient was a markedly chlorotic girl, eighteen years of age, who was attacked by total blindness whenever she was constipated and strained during defecation; these attacks were sometimes easily combated by the dorsal position, with moderate depression of the head and elevation of the lower extremities, or by applying broad bandages about the limbs in order to force the blood upward. When these measures failed the blindness lasted from four to six hours, without interruption, and then gradually disappeared. Repeated careful examinations of the eyes revealed a marked paleness of the retina, pulsation of the veins and arteries, a transparency of the vessels, and a concentric diminution of the visual field for all colors.

At this place the author wishes to express his best thanks to his colleague, Dr. Eversbusch, of Erlangen, who was good enough to work out a small collection of the ocular disturbances and diseases which occur in chlorosis. The notes he so kindly furnished are published unchanged:

"The ocular diseases occurring in chlorosis are usually partly or wholly due to the state of weakness caused by the underlying disease. This is specially true of the weakness of accommodation, which is prone to occur when the eyes are hypermetropic. This is not infrequently combined with a hyperesthesia, in consequence of which all constant close work produces asthenopic symptoms. The complaints of bad vision and of flickering before the eyes are frequently also due to decreased retinal energy, which manifests itself as asthenopia retinalis, as hemeralopia, or as a concentric diminution of the visual field.

"The ocular background is more or less pale. An exact decision in this respect, however, is more or less difficult, since the color of the optic disc and of the chloroid membrane is subject to great physiologic

variations. Nevertheless, there are cases in which the fundus oculi seems unusually pale. The most striking phenomenon, however, is the transparency of the retinal vessels; where two vessels cross, the contours of the one may be distinctly made out through the walls of the other—something which is not seen in the normal eye. Under normal conditions, moreover, the vascular walls are not visible, while in chlorosis both the arteries and the veins of the retina give a bright reflex, sometimes narrow and faintly outlined, sometimes broader and more distinct. Pulsation is observed not only in the retinal veins in their course through the optic disc and the adjacent portions of the retina, but as a result of the marked diminution of blood-pressure the retinal arteries also pulsate spontaneously, and there is a more or less distinct movement in their peripheral ramifications. Sometimes, strange to say, there is present a marked degree of arterial hyperemia, so that the vessels are of a normal red color and the total cross-section of the arteries in the optic disc seems to be larger than normal. Such conditions are found even in eyes which are otherwise perfectly healthy.

"Sometimes there is observed a pronounced neuritis and neuroretinitis, with or without degenerative changes (more or less numerous, irregular hemorrhages and reddish-gray, yellowish-white or whitish spots of exudate), and these may be so distinct that the appearance simulates that of nephritic neuroretinitis. Gowers and William state that they always found a mild degree of hypermetropia in their patients. Since a slight congestion of the optic disc is often present in such cases, it is quite possible that this might intensify the neuritic changes caused by the condition of the blood.

"Edema of the lids is also worthy of mention. The lower lids are particularly affected. The edema may disappear spontaneously with the improvement of the general condition, or like the neuroretinitic change rapid disappearance and complete recovery may follow the administration of iron.

"Scleritis, which is not uncommon in chlorotics, is a much more serious affection. Seroplastic iridocyclitis and exudative (non-purulent) choroiditis, which are characterized by photophobia and more or less marked opacities of the vitreous humor, may sometimes be, at least indirectly, due to chlorosis. They are worthy of particular attention, since they may cause permanent opacities of the cornea and of the lens, and gradually produce blindness as a result of a detachment of the retina.

"Finally, trigeminal neuralgias, particularly of the supra-orbital branch, may be encountered in chlorosis, and these are often combined

with vasomotor symptoms in the areas supplied by the diseased nerves."

In concluding, the author will give a short series of statistics from his own clinical records. Careful examinations of the eyes, mostly under the control of specialists, were made in 46 cases of chlorosis. Disregarding congenital anomalies and ocular diseases that could have had nothing to do with chlorosis there was found:

A normal condition in 22 patients.

Unusually pale retinæ and transparent vessels in 17 patients.

Arterial pulsation outside of the papillæ in 5 patients.

Venous pulsation in 3 patients.

Choroiditis pigmentosa in 1 patient.

Diffuse white spots in the vicinity of the papillæ in 1 patient.

Concentric diminution of the visual field in 7 patients.

[Englehardt[1] reports a case of chlorosis in a girl of eighteen, in which optic neuritis and symptoms suggestive of brain tumor developed. There was at first poor vision, dilated and non-reactive pupils, swollen optic papillæ surrounded by hemorrhages and white streaks, a loss of the sense of smell, and weakness and paresthesia of the right hand and arm. Later epileptiform seizures developed; paresis of the right facial nerve, increasing weakness and anesthesia of the right arm and right side of the body. Loss of temperature-sense and diminution of the sense of pain came on. Finally the patient died, and at the autopsy no lesion of the brain was found, but simply evidences of general anemia and a dry condition of the brain substance.

In a similar communication by Neave[2] is recorded a case of chlorosis in a woman of thirty-one, with symptoms strongly suggestive of cerebral thrombosis, but the patient eventually recovered.—ED.]

THE SKIN.

The condition of the skin in chlorosis has already been discussed. We refer to the section upon General Symptomatology and to the description of the chlorotic disturbances of the circulation. Nevertheless, it may be well to briefly review what has previously been said.

The following cutaneous phenomena are observed:

1. **Anemia of the Skin.**—Apart from the general pallor of the skin and its greenish-yellow tinge (see page 363), we would mention the occurrence of angiospasms, which render anemic the individual peripheral districts (fingers, hands, feet, leg, tip of the nose) for varying

[1] *Münch. Med. Woch.*, No. 36, 1900. [2] *Lancet*, July 28, 1900.

periods of time, and which are usually accompanied by paresthesias, by hyperesthesias, or by actual pain (see pages 362 and 396).

2. **Hyperemia of the Skin.**—The tendency to temporary dilations of the blood-vessels is in marked contrast to the paleness of the skin. These fleeting hyperemias usually affect the face and the upper part of the chest. The frequency of their occurrence varies greatly with the individual patient (see page 357). In many chlorotics there is a permanent hyperemia of the skin of the face; this condition is designated as "chlorosis rubra." In other patients, the hands, and particularly the fingers, are the seat of a temporary or of a permanent hyperemia. Sometimes there is marked pain in addition to the congestion of the skin of the finger, and this condition is known as erythromelalgia (see page 397).

[Marked flushing of the skin may quickly give place to an ashy pallor under excitement, anxiety, etc. One writer has referred to this variety as palpitation in the capillary circulation.—ED.]

3. **The Secretion of Sweat.**—In chlorosis the amount of perspiration is by no means uniform. In the majority of cases anomalies are not to be observed. The secretion is frequently diminished, and, still more frequently, increased. Many chlorotics complain of sweating of the hands, in the axillæ, and between the breasts. In some instances there is general hyperhidrosis. In 250 cases of chlorosis, we find excessive sweating recorded 9 times; in 5 cases this symptom disappeared with the cure of the disease.

4. **Anomalies of the Secretion of Fat.**—Seborrhea is frequently found in chlorotics.

5. **Exudation.**—Urticaria is more common in chlorotics than in healthy young girls. In 6 of the 250 clinical records, the tendency to urticaria is expressly emphasized. In addition the author must also mention 2 cases in which urticaria factitia could be produced at any time during the height of the chlorosis; this was impossible after the patients recovered from the disease. The occurrence of edema has been mentioned on page 402.

6. **Chronic eczemas** can scarcely be brought into etiologic relation with chlorosis. Nevertheless, if they are present, they are dependent upon the disease to a certain extent, since they grow better and worse with corresponding variations in the course of the chlorotic process.

7. **Acne simplex** is a very frequent complaint and brings to the dermatologist many chlorotics who scarcely consider their other symptoms. The seat of predilection is the face, particularly upon the fore-

head, though it also occurs upon the neck and shoulders. Acne indurata is frequently present. In this case the acne pustules must be opened; while in simple acne, iron and arsenic in combination with the hygienic and dietetic treatment of the chlorosis have proved themselves to be the best therapeutic measures.

8. **Purpura rheumatica** is a rare complication of chlorosis. Cases of this character have been repeatedly observed by our colleague Dr. Carl Herxheimer; they rapidly recovered when placed upon preparations of iron.

9. **Pigmented Hypertrophies of the Skin Resembling Chloasma.**—These spots are found upon the forehead, eyebrows, temples, cheeks, upper lip, and chin. These pigmentations come and go; when present they are very resistant to treatment and only gradually disappear after the complete cure of the chlorosis.

10. **Trophic changes in the nails and hair** (falling-out of the hair, white spots in the nails, brittleness of the nails), though occasionally observed in chlorosis, are much rarer than in other forms of severe anemia.

11. **Chilblains of the feet** must also be mentioned at this place (see page 397). For the relief of this annoying and painful affection, the authors can warmly recommend inunctions of an ointment of calx chlorata—calx chlorata 1 gm. (gr. xv), ung. paraff. 10 gm. (ℨijss)—together with rubbing and massage.

THE NERVOUS SYSTEM.

The mutual relations between chlorosis and the nervous system have been frequently discussed in the earlier portions of this monograph. These relations are reciprocal, since chlorosis favors the outbreak of psychic peculiarities, general necroses, and neuralgias in individuals with neuropathic tendencies; vice versa, a diseased nervous system which is weakened in certain directions will allow of the marked predominance of individual symptoms of chlorosis, consequently favoring the impression that these symptoms, dependent upon the nervous system, are the chief trouble, and that the chlorosis is but a subsidiary affection. While admitting this and recognizing that chlorosis is accompanied by many symptoms which are also well-known signs of a neuropathic predisposition, some authors go still further, claiming that chlorosis is a neurosis and that all its individual symptoms, deficient blood-formation included, are immediately dependent upon the diseased nervous system. This theory, which has already been repeatedly mentioned, does not seem to be worthy of a serious discussion.

The psychic condition of chlorotics and the nervous anomalies in the circulatory, respiratory, and digestive organs have been fully considered at pages 361, 389, 397, 404, and 406.

It will be sufficient to review briefly the most important anomalies of the nervous system that are dependent upon chlorosis, or that are independent affections complicating the course of the disease.

1. **Psychoses.**—It has been repeatedly pointed out that chlorosis diminishes the activity of the mental faculties in general and produces a condition of irritable weakness similar to mild neurasthenia. The degree in which the weariness and irritability are present varies greatly and depends upon the particular disposition of the patient. A parallel between the severity of the anemia and the severity of the psychic alterations is not to be observed. More exact psychophysic investigations in reference to the degree and progress of these disturbances are as yet wanting.

More marked conditions of exhaustion may proceed from these milder disturbances, particularly in the form of acute dementia; milder grades may occasionally be due to chlorosis; this condition much more rarely results from idiocy.

In youthful individuals who are predisposed to periodic insanity chlorosis may sometimes be responsible for the first attacks, which are in the form of melancholia. These may disappear completely for a time, but again make their appearance upon certain occasions later in life. Since this mental affection is usually dependent upon constitutional predisposition, and only the individual attacks are due to external conditions, opinions are naturally divided in reference to the importance of the influence of such exciting causes. Nevertheless, it can not be denied that a pronounced disturbance of nutrition, such as that produced by chlorosis, is sometimes of importance for the development of the first attacks. Periodic insanity, a mental disturbance which is thorough constitutional, and the attacks of which usually have a definite inherited character, is not further influenced by the course of the chlorosis; the paroxysms once introduced, pursue an independent course.

The acute curable forms of mental disturbance, on the contrary, are dependent upon the course of the chlorosis, inasmuch as they are caused by the chlorosis and by the nutritive anomalies which are associated with the disease. The mental affection disappears with increasing improvement of the physical condition.

2. **Hysteria** in its manifold forms is by far the most frequent anomaly of the nervous system which is encountered in chlorosis. It is difficult to formulate an accurate opinion upon its occurrence, since

the conception of hysteria is so largely dependent upon the individual making the diagnosis, and since it is also important to consider the locality and the class of society in which the patient is found. On the whole, almost every physician has the impression that hysteric symptoms are much more frequent in chlorotic than non-chlorotic women of the same age and of the same position in life. These hysteric phenomena are usually unimportant; we may even be in doubt as to whether the anomalies of sensation, of the disposition, and of the will are to be regarded as the results of hysteria or as the natural consequences of the physical discomfort and weakness.

Hysteria more rarely manifests itself in abnormalities of function of individual organs or of circumscribed portions of the body. The figures given below can naturally make no claim to universal application, since they were largely obtained in hospitals, and the character of the material under observation was consequently limited.

Of 255 chlorotics, 30 had pronounced hysteric symptoms as indicated in the table. These hysteric symptoms were as follows:

Hysteric paralyses of the extremities	5 times.
" laryngeal paralyses (aphonia)	3 "
" mutism	2 "
" convulsions	6 "
" catatonia	1 time.
" hemianalgesia	7 times.
" circumscribed analgesia	2 "
" anesthesia of the pharynx	10 "
" vagus neurosis (v. Noorden)	4 "
" insanity	1 time.
" globus	12 times.
" dysuria	3 "
" tachycardia	20 "
" tachypnea	13 "
" vomiting	9 "

3. **Neuralgias.**—By true neuralgias we do not mean the occasional occurrence of pain in this or that set of nerves, but a chronic diseased condition with exacerbations, remissions, and pauses. Such true neuralgias are rare in chlorosis, corresponding to the infrequency with which such neuralgias are encountered in individuals of the same age as chlorotic patients. They may constitute a purely accidental complication and are then scarcely, if at all, influenced by the course of the chlorotic process. In other instances they are strikingly dependent upon chlorosis; they come and go with the disease and their intensity is dependent upon its variations. They react, as does the anemia, to the administration of iron, and sometimes still better when the iron is combined with arsenic. The favorite location of neuralgias dependent upon chlorosis is the region supplied by the trigeminus, particularly by the ophthalmic division.

The following statistics will show the frequency of the neuralgias. Of 255 chlorotics :

Neuralgias of the ophthalmic division of the fifth nerve		3
" " inferior maxillary division of the fifth nerve		2
" " brachial plexus		2
Mastodynia		2
Sciatica		1

4. **Chorea minor** is not to be regarded as a neurosis intimately associated with chlorosis, but it manifests itself as an independent complication. It can not be denied that chlorotics show a certain predisposition for chorea; among adult females with chorea there are many who are at the same time chlorotic. The tendency of chlorotics to develop chorea in hospitals may sometimes be very distinctly demonstrated. In the Second Medical Clinic of Berlin the author has repeatedly observed how chorea spread from one patient to several others, showing particular preference for chlorotics. We, therefore, insisted upon placing the girls with St. Vitus' dance as far as possible from their chlorotic companions in the same ward.

[C. W. Burr studied the blood of a series of cases of chorea, and found that anemia and chlorosis are much less frequent and pronounced than is usually believed.—ED.]

Other anomalies of the nervous system, which manifest themselves in various portions of the body, will be found discussed in other sections.

THE STATE OF NUTRITION. METABOLISM. THE CONDITION OF THE URINE.

BODY-WEIGHT.

According to the statements of the text-books, chlorosis does not interfere with nutrition in general. It is, of course, pointed out that the disease shows a particular preference for individuals whose physical development has been somewhat retarded, girls with thin slender bones and with a deficient development of the muscles and of the adipose tissue. Quite independently of this, the additional question as to whether chlorosis is prejudicial to the condition of nutrition is answered in the negative. We frequently find the statement that chlorosis is accompanied by relaxation and deficiencies of the musculature, but that it favors the development of the panniculus adiposus. These statements are explained by reference to some of the older investigations upon metabolism by J. Bauer,[191] Jürgensen,[192] and A. Fränkel,[193] who found that experimental anemias caused an increase of albuminous decomposi-

tion (or of muscular atrophy) and a diminution of the respiratory interchange of gases (or a diminution of the metabolism of the fats).

We have nothing to add to the general opinion which is prevalent in the literature upon the subject. From our own observations, which have been directed particularly to this point, it can not be said that chlorosis exercises a deleterious influence upon the general nutrition. It is true that many chlorotics are seen, in hospitals and in private practice, who not only have been originally poorly nourished and who continue to be so throughout the course of the disease, but who, though previously well-developed, suffer from loss of weight, loss of fatty tissue, and relaxation of the muscles during the chlorotic attack. At least one-half of the patients who enter hospitals have suffered from such more or less pronounced losses; in the better classes, such a condition of affairs is much less frequent.

In 72 clinical histories we found statements in reference to the previous condition of the general nutrition:

Among these 29 had retained their corpulence and body-weight in spite of the disease. Of these 13 were treated in private practice, 16 were in hospitals.

In 35 patients there was a decided loss in corpulence and body-weight during the disease (6 from private, 29 from hospital practice). In 8 patients a considerable gain in weight occurred during the course of the disease (6 from private, 2 from hospital practice).

[Houston[1] has shown that the fluctuations in weight are largely dependent upon the degree of hydremia of the blood and tissues.—Ed.]

The chlorosis is less responsible for the retrogression of the nutritive processes than are certain subsidiary circumstances—the neglect of treatment, exhausting occupations when the capacity for work is diminished, and, particularly, food that is not adapted to the diseased condition. We can not expect chlorotic girls to do themselves justice at the family table, in spite of their many annoying symptoms, which are sometimes constant and sometimes of a most variable and intermittent character. If the necessary attention is not paid to this point, as is so frequently the case from social, pecuniary, or other reasons, the chlorotics do not receive sufficient nourishment and consequently lose in weight. The rapid improvement caused by suitable food shows that this emaciation is the result of unfavorable external conditions, and not of the disease. If the food is of the proper quality and given at appropriate intervals, with regard for the demands of the diseased organism, the amount need not be excessively increased nor must it necessarily con-

[1] *Brit. Med. Jour.*, June 14, 1902.

tain an increased number of nutritive units (calories), in order to rapidly cause an improvement in the body-weight.

In 75 clinical histories (not picked cases) from the Second Medical Clinic of Berlin, we found the following statements in reference to changes in the body-weight within the two or four weeks of treatment:

The weekly increase of weight was

0.2–0.5 kg.	(0.44–1.1 pounds)	in 15	patients.
0.5–1.0 "	(1.1–2.2 ")	" 29	"
1.0–1.5 "	(2.2–3.3 ")	" 17	"
1.5–2.0 "	(3.3–4.4 ")	" 7	"
2.0–2.5 "	(4.4–5.5 ")	" 2	"
2.5–3.0 "	(5.5–6.6 ")	" 3	"

In 2 instances there was a decrease of body-weight.

We will return to the condition of nutrition in general after the consideration of the investigations in reference to the interchange of gases and the metabolism of the albumins.

THE RESPIRATORY INTERCHANGE OF GASES.

There was formerly a universal supposition, based upon the experiments of J. Bauer,[191] that anemia decreases the absorption of oxygen and the production of carbonic acid; in other words, the entire metabolic process. Accurately speaking, this theory is applicable only to the acute anemias of animals (after venesection), but it has been readily transferred to all clinical forms of anemia. In the meantime, the faultless investigations of Gürber[194] have demonstrated the untenableness of the former conception. The process of combustion remains normal not only immediately after prolonged bleedings, but permanently so—*i. e.*, until the previous hemoglobin percentage has been reëstablished. There was, if anything, a slight increase, rather than a decrease, of the combustion of oxygen. We lay no special value upon animal experimentation when it is utilized to explain the symptoms of chronic disease. Much more important are the exact determinations of the respiratory interchange of gases in chlorotic individuals.

Author.	O consumed per kilo per minute.	CO_2 eliminated per kilo per minute.	Respiratory quotient.
F. Kraus[195]:			
Observation 1	5.110 c.c.	3.700 c.c.	0.722
" 2	5.480 "	4.000 "	0.727
" 3	5.710 "	4.250 "	0.742
Bohland[196]:			
Observation 1	4.620 "	4.200 "	0.910
" 2 { in the beginning	5.308 "	5.007 "	0.940
" 2 { later	3.056 "	2.866 "	0.940

The experiments were carried out according to the procedure of Geppert and Zuntz, which has proved itself to be of great value in the

solution of important clinical and physiologic questions. In order to appreciate these tables we must be familiar with the normal figures. In healthy individuals of moderate weight, who are fasting and at rest—*i. e.*, under the same conditions as existed during the above-quoted experiments—we find the following values:

O consumed 3.5–4.5 c.c. per kilo per minute.
CO_2 eliminated 2.5–3.5 " " " " "

In these experiments the deciding weight is always to be placed upon the consumption of oxygen, since the elimination of the CO_2 produced is not always uniform, and the normal respiratory quotient is consequently subject to considerable variations. In complete contradiction of the previous views, we consequently find that the respiratory interchange of gases in chlorosis is rather increased than diminished. Investigations in other anemias gave the same result (pernicious anemia, leukemia, secondary anemia of carcinoma, anchylostoma anemia) a slight increase of all the processess of oxidation, consequently, seems to regularly accompany all anemic conditions. We would explain this by recalling the fact that the anemic quality of the blood increases the work of the heart and of the respiratory apparatus. The experiments, however, are not sufficient to determine whether the increased work of the heart and of the respiratory muscles are of themselves sufficient to explain the increase of the respiratory interchange of gases. In chlorosis there are still other factors to which attention must be devoted. Chlorotics not infrequently have an enlarged thyroid gland and present other symptoms which remind us of rudimentary Basedow's disease. Now, we know that in artificial thyroidism (administration of thyroid gland) and in natural thyroidism (Basedow's disease) the processes of oxidation are increased. Still, further investigation is necessary in this fruitful field of labor to determine whether the thyroid gland has not an influence upon the increase of the processes of oxidation in chlorosis.

THE METABOLISM OF THE ALBUMINS.

Like the views in reference to the respiratory interchange of gases, the theories of the metabolism of the albumins were for a long time dominated by the results of animal experimentation. The first, and up to this time the only, experiment which attempted to solve this question at the bedside was made by Lipman-Wulf[75] under the authors' direction.

Case 1. Ella B., seventeen years of age; weight, 43. kg. (94 lb.). At the time of the experiment the blood contained 2,500,000 red blood-corpuscles to the c.mm. The dried residue of the blood amounted to 15.35 per cent., which corresponded to about 6 per cent. of hemoglobin.

Case 2. Alma L., seventeen years of age; weight, 60 to 61 kg. (132–134 lb.). The dried residue of the blood amounted to 15.1 per cent.

Case 3. Bertha L., twenty years of age; weight, 60½ to 62 kg. (133–136.4 lb.). The blood contained 3,750,000 red blood-discs and 8000 leukocytes to the c.mm. The dried residue of the blood was 13.1 per cent., corresponding to 4.5 to 5 per cent. of hemoglobin.

Case.	Food daily ingested.			Calories per kg.	Daily elimination of N.	Duration of experiment.	Nitrogenous balance for the entire experiment.
	N.	Fat.	Carbo-hydrates.				
1	12.90 gm.	86 gm.	204 gm.	about 38.0	12.8 gm.	7 days.	0.403 gm.
2	13.06 "	98 "	250 "	" 37.0	12.7 "	7 "	2.597 "
3	12.78 "	94 "	240 "	" 37.6	12.7 "	5 "	0.474 "

From the figures of the table, we would claim that there is a nitrogenous equilibrium upon the ingestion of albumins and an average diet; the metabolism of the albumins was entirely normal. We regard the question of the metabolism of the albumins in the ordinary cases of severe chlorosis as solved by these observations, the smallest details of which were accurately carried out and free from every possible objection, but think that the investigation should be further extended to those cases which present, in addition, the symptoms of Basedow's disease. The absence of every pathologic decomposition of the albumins in our cases would theoretically indicate that destructive toxic effects upon the protoplasm of the patients play no rôle in the disease. We mention this, since many authors trace chlorosis to an enterogenic intoxication.

In addition to the investigations of Lipman-Wulf, Schücking has also experimented upon the subject of metabolism; unfortunately, this work was unknown to us at the time of Lipman-Wulf's publication. The experiment of Schücking[196a] does not positively show that the metabolism of the albumins was normal in his patient.

THE GENERAL NUTRITIVE CONDITION.

We have seen that many chlorotics emaciate during the course of the disease, and have traced this to unfavorable conditions of the diet. We have also agreed with the statements of other authors that some chlorotics become stouter and gain in weight during the course of the disease. What is the explanation? If the patients gain in weight the nutritive supply must be greater than the demand—the gain in potential energy is greater than the output of actual force (work and heat). Which factor is responsible for the disturbance of the condition of

equilibrium in these cases? In most cases the cause is to be found in both factors.

In considering the output, the diminution of the energy of oxidation can no longer be considered; under the same external conditions chlorotics consume just as much material as do healthy individuals (see p. 444). The causes must be sought elsewhere. The majority of the chlorotics who gain markedly in weight during the course of the disease, particularly in the independent classes, do not expend a great deal of muscular energy. They sleep late, rest frequently during the day, and limit their movements on account of the ready appearance of fatigue, so that they perform a smaller amount of work than do their fellows of the same age under similar conditions of life. To this is added a diminished radiation of heat from the surface of the body. The skin of chlorotics is anemic to a marked degree; the cutaneous vessels are of small caliber, and the patients are consequently subject to sensations of chilliness, which may be increased to icy coldness if there is added a spasmodic contraction of the cutaneous capillaries. The chlorotics, chilling easily, like to clothe themselves warmly and cautiously avoid exposing themselves to cold. They voluntarily limit the radiation of heat, and the cutaneous cells, consequently, do a less amount of work. In order to avoid being misunderstood, the author must again point out that when external conditions are exactly the same no difference can be found in the combustion of material in healthy and in chlorotic individuals (same combustion of O, see above). Chlorotics, however, voluntarily and involuntarily produce different external conditions, and their total production of heat and of living energy is less than the average.

Let us now consider the other factor in the question—the nutritive supply. If we carefully determine what these patients who take on flesh actually eat, and calculate the caloric value of the food ingested, we always obtain nutritive values which readily explain the increase in weight. A chlorotic individual who subjects herself to little physical effort requires for her maintenance a diet which furnishes only about 34 to 38 calories per day per kilogram (2.2 lb.). In those chlorotics who had gained weight before they came under treatment, and who were still gaining, we could always calculate a much higher caloric value of their diet. These cases were usually girls in well-to-do families, where it was insisted upon that the chlorotics should drink a considerable quantity of the very best quality of milk. This is a feature of the present time. The milk cure is, indeed, regarded as a universal remedy, and the amount often consumed is astonishing. If we reflect

that 1 L. (1.056 qt.) of good rich milk has a nutritive value of about 640 calories, and further consider that many chlorotics drink 2 L. (2.112 qt.) and more per day without any particular medical advice, we see that the patient receives about 1280 calories from this source alone. A girl weighing about 55 kg. (121 lb.) does not require more than 2100 calories at most. A very small quantity of other food needs to be added to the 2 L. of milk to supply the remaining 800 calories, and anything beyond this must result in the gain of so much adipose tissue.

From our investigations we must assert that chlorotics tend to store up adipose tissue, because they try to limit the amount of work performed and the heat produced, with no corresponding diminution of the amount of food ingested, sometimes even increasing it above the normal average. This well-known phenomenon is consequently due to the working of a very simple formula and the subject is freed of all mysticism.

THE METABOLISM OF HEMOGLOBIN AND OF IRON.

We now enter upon a domain which has been rather thoroughly explored in a certain direction in recent years and in which, until a short time ago, the greatest confusion existed. In another direction, however, there has been almost no scientific work. We may expect great results from its thorough investigation, which will be of material value in formulating a correct theory as well as in the prophylaxis and treatment of the disease.

In the chlorotic process, as has been previously stated, the hemoglobin percentage falls, and, in the second place, there is also a decrease of the number of red blood-cells. How are the oligochromemia and the oligocythemia produced? They may naturally be assumed to occur in three ways:

1. A more marked destruction of hemoglobin, or of the corpuscles.
2. Diminished formation.
3. A combination of both processes.

The question has appeared and reappeared ever since chlorosis has had a literature. Many answers have been given; the most frequent one—particularly in the older medical classics—was that the chief fault was to be found in the formation of the blood. To our mind it seems of little purpose to detail all the theories and hypotheses that have had an influence in answering this important question. We must lay all theories aside and consider only those few points that are firmly established and which may furnish the basis of further investigation.

Significance of Blood Examinations.—In the present state of our knowledge the condition of the blood can furnish us with no in-

disputable evidence. The isolated occurrence of nucleated blood-discs (normoblasts, see p. 375) would, indeed, indicate attempts at regeneration; if anemia develop, in spite of active regeneration of the blood, the destruction of the blood must, of course, be abnormally increased. As a matter of fact, the occurrence of normoblasts has been utilized in the defence of that theory (Dunin [11]) which traces the chlorotic quality of the blood to increased blood-destruction. A few scattered normoblasts do not prove that a general regeneration of the blood is in active progress in all of the blood-forming organs; this regeneration may be active in certain localities, and yet the process, as a whole, may be far below the normal. In the second place, we might theoretically utilize the fact that the hemoglobin is decreased much more than the number of red blood-corpuscles. In those anemias which are undoubtedly dependent upon blood-destruction (so-called pernicious anemia, secondary anemias from infections and intoxications) we observe a much greater decrease of the number of corpuscles than of the hemoglobin. A certain antithesis, at least, of the extremes—fresh cases of pure chlorosis and of pernicious anemia—is unmistakable. Further investigation is necessary before we can decide that the principal difference of the anemic processes is to be found in the two extreme types of blood.

Losses of Blood.—Another method for the solution of this question is offered by the investigations upon the metabolism of hemoglobin. The work of H. v. Hösslin [197] marks the first advance in this direction. His first idea was that in chlorosis there was no indication of an increased destruction of the corpuscles within the blood-vessels, but that the blood showed a great resemblance to that resulting from external hemorrhages. v. Hösslin correctly lays no great weight upon the menstrual losses; they are common to all women, and as long as they remain within normal limits they can not be made responsible for the anemia; moreover, amenorrhea and scanty menses are much more frequent in chlorosis than is the opposite condition of affairs. v. Hösslin suspects the gastro-intestinal canal of being the site of the losses of blood, these losses proceeding from the frequent complication of chlorosis with gastric ulcer and other gastric affections. By examination of the feces, v. Hösslin found the following amounts of iron:

	Average weight per gram of dried feces. Iron.	Iron as hematin.
9 healthy girls	0.38 mg.	0.0260 mg.
3 " men	0.77 "	0.0430 "
26 chlorotics	0.47 "	0.0280 "
11 "	1.13 "	0.1675 "
5 "	2.34 "	1.1330 "

Greater weight is to be laid upon the values of the first column than upon the amounts of iron appearing as hematin, since the quantitive determination of the latter can not be exactly carried out. The figures seem to speak for the supposition of v. Hösslin: that hemorrhages into the gastro-intestinal canal of chlorotics are frequent. To conclude that these hemorrhages are the cause of the chlorotic anemia is, however, quite another thing. Quite independent of the accuracy of the conclusion, we can not regard as established his most important premise, the increased amount of fecal iron. The determination of the amount of iron in the dried feces is by no means sufficient for this purpose; the only reliable guide is the amount daily excreted, an accurate control being kept upon the food ingested. Such investigations have not as yet been made. We must consequently regard the publications of v. Hösslin more as a welcome stimulus to new work than as complete additions to the pathology of chlorosis.

Hydrobilirubin.—The investigations upon the excretion of the derivatives of hemoglobin, which arise within the cells of the body, were carried somewhat further. The liver is the chief, and probably the only, place in the body where the hemoglobin molecule is normally decomposed: the colored constituent, the hematin, is here further split up into iron, on the one hand, and bilirubin on the other. The bilirubin is excreted. The iron remains partly in the liver and partly in other organs, probably in the form of ferratin, or some similar combination, to be used later for the purpose of blood-formation; very small quantities gradually find their way through the intestinal wall and through the kidneys and appear in the excretions. In determining the metabolism of hemoglobin, both bilirubin (non-ferruginous) and its derivatives, as well as the iron itself, may be considered.

The formation of primary biliary pigments and the excretion of bilirubin certainly maintain an approximate parallel with the destruction of hemoglobin (Stadelmann [196]); unfortunately, we can not say the same of the bilirubin derivatives which are excreted by the intestine and by the kidneys. The most important derivative and the one present in the largest quantity is hydrobilirubin (in the urine, known as urobilin). Both urine and feces also contain other substances related to the biliary pigments, particularly the so-called chromogens (urobilinogens). They do not escape the quantitative determination, since the preparatory treatment of the feces and urine (heating with acids) converts them into the true pigments. Hematoporphyrin is also a derivative of hemoglobin; with the exception of certain diseases, however, it is excreted in too small an amount to be taken into consideration.

Although the determination of the amount of urobilin—partly in the form of known, partly in the form of unknown substances—allows of the escape of certain amounts of bilirubin derivatives, and, although the urobilin is by no means an accurate measure of the metabolic changes of the hemoglobin, the following statements may be assumed to be correct.

If many biliary pigment derivatives and their congeners (hematoporphyrin) are found in the urine and feces, there is a great destruction of hemoglobin; if few such derivatives are present, the destruction of hemoglobin is slight.

Investigations upon this subject are still few in number: G. Hoppe-Seyler[199] found an average of 0.123 gm. of hydrobilirubin in the twenty-four hours' urine of healthy individuals; in chlorosis he observed—0.03, 0.05, 0.124 gm. A. Garrod,[200] who examined 8 cases of chlorosis, states that, as a rule, the urine was pale and poor in pigment; the urobilin and hematoporphyrin were never increased. In 5 cases of severe chlorosis we determined the amount of urobilin in the urine (method of G. Hoppe-Seyler, with slight modification); the analyses were made with the mixed urines obtained on two successive days. The daily amounts in the five cases were:

1. Imponderable traces.	3. 0.012 gm.
2. " "	4. 0.019 gm.

5. Imponderable traces.

In the first and third cases the amount of hydrobilirubin in the feces was estimated at the same time. The feces were treated with hydrochloric-acid alcohol and kept at a boiling-point until no more pigment was given up; the amount of hydrobilirubin in the extract was then determined. In these 2 cases there were 21 and 29 mg. of hydrobilirubin respectively. It should be mentioned for comparison that in a case of pernicious anemia the urine furnishes 0.153 gm., and the feces 0.92 gm. of hydrobilirubin.

Although these scanty figures do not allow us to draw any far-reaching conclusions, they certainly speak against the assumption that chlorotic anemia is due to the increased destruction of hemoglobin.

The Metabolism of Iron.—The question as to whether the anemia is due to the deficient formation of hemoglobin or to the increased destruction of hemoglobin, finds still less of a solution from the investigations upon the metabolism of iron. v. Hösslin's one-sided analyses of the feces are lacking in demonstrative proof. The decision must be made dependent upon exact determinations of the iron ingested and the iron eliminated. Such experiments are most trying to the patience

of the investigator and of the chlorotic. It is not sufficient to determine the balance of iron for one or several days, but the investigation must be carried out for longer periods of time. The quantitative relations between the iron ingested and the iron eliminated are complicated by the fact that certain amounts of iron, both from the decomposing hemoglobin as well as from the food, remain in the body (liver, spleen) to be gradually eliminated at a later period. In long periods of observation this peculiarity is not a disturbing factor; short periods, however, are incapable of furnishing clear proof. At the present time we know of no investigations upon the balance of iron in chlorosis.

We must consequently limit ourselves to the discussion of certain points in reference to the metabolism of iron which are partly of a historical and partly of a practical significance for the critical study of chlorosis. It is not our intention to discuss the "iron question" with all its details. For such information the reader is referred to the works of Bunge[161] (1889), Kobert[201] (1891), v. Noorden[202] (1893), Bunge-Quincke[1] (Congress for Internal Medicine, 1895), Quincke[203] (1895), and Quincke-Hochhaus[204] (1896).

In former times there was scarcely a doubt that the iron salts were absorbed from the intestinal canal, but in the course of the eighties such absorption was actively denied. After the administration of iron, it was found in the feces, but only sparingly or not at all in the urine (experiments upon man and animals). On the other hand, it was established that certain highly constituted ferruginous combinations in the urine were increased, and, consequently, absorbed from the intestinal canal. This was first observed in reference to Bunge's hematogen, a nucleo-albumin containing iron; proofs were furnished later of the absorption of Kobert's hemol and hemogallol, substances which are obtained by the action of reducing agents upon the hemoglobin or upon the blood, and which, like hematogen, hold the iron in such strong combination that it is not accessible to the customary reagents (ammonium sulphid, potassium ferrocyanid). At the close of the eighties it was believed that only the complicated organic combinations of iron, such as occur in vegetable and in animal substances (the so-called ferruginous nucleo-albumins and the proteids containing iron) were adapted to absorption from the intestine, and that these alone could be employed for the construction of the hemoglobin. The inorganic and organic iron salts, as well as all the organic combinations of iron in which the iron was but loosely combined, were said by many to be incapable of absorption and devoid of any therapeutic power. The representative pharmacologists (Schmiedeberg, Bunge, Kobert, and their followers) gave

out statements which were calculated to make it appear as though the practising physician had been greatly deceived for many years in reference to the theoretical and practical significance of the iron therapy. It can be well understood with what readiness, not to say enthusiasm, the theory of Bunge was received by physicians. It took into consideration both the newer teachings of the pharmacologists as well as the practical curative results of the administration of iron. Bunge believed that the ferruginous nucleo-albumins of the diet were usually sufficient to meet the demand of the body for iron. In chlorosis, however, as a result of a diminished gastric secretion of hydrochloric acid, the processes of decomposition were increased, giving rise to much H_2S, which separated the iron from the nucleo-albumin and combined with it to form insoluble sulphid of iron. If these patients were given inorganic or organic salts of iron, the H_2S combined with them and spared the iron of the nucleo-albumins. The nucleo-albumins were then absorbed unchanged and had a therapeutic effect. The theory became untenable when it was found that:

1. The gastric hydrochloric acid, as a rule, is not diminished in chlorosis (see p. 418).

2. The decomposition of the albumins in the intestine is only exceptionally increased (see Rethers,[132] and p. 422).

3. Even sulphid of iron has a curative influence in chlorosis (R. Stockman[205]).

The theory, upon which Bunge himself lays no great weight at the present time, became superfluous when proof was furnished that the inorganic salts of iron are actually absorbed, and that the absorption is by no means limited to the ferruginous nucleo-albumins.

The history of the discovery of such proof is very interesting. It was first observed that iron which gained access to the circulation (subcutaneous injection) was either not excreted by the kidneys at all or at least only in traces, but that it accumulated in the liver and in the spleen. Both organs seem to attract the circulating iron as though they were magnets (Kobert); they are the places for the storage of superfluous iron. From these places the iron is very gradually removed at irregular intervals, and the greater portion is eliminated through the feces and not through the urine. The intestinal wall is the actual site of the excretion of the iron. We should no longer wonder when we observe that the amount of iron in the urine is not increased after the administration of this substance. It is evident that the conclusion formerly drawn from this observation—that the salts of iron are not absorbed—was both hasty and untenable.

Positive proof of the absorption of iron was, however, still wanting. This was furnished almost simultaneously by the investigations of Gottlieb [206] and of Kunkel.[207] Gottlieb fed dogs, Kunkel mice, with iron salts, and they both found the liver, as well as the entire body, much richer in iron than was the case in the control animals, who received exactly the same diet, but no iron salts. These experiments (with some unimportant modifications) were repeated by Woltering [208] and by Cloetta,[209] and the results of Gottlieb and of Kunkel were confirmed. In the meantime, Macallum,[210] W. S. Hall,[211] J. Gaule,[212] and Hochhaus-Quincke [204] succeeded in demonstrating, by means of microscopic specimens, the absorption of iron in the duodenum and its passage through the intestinal villi. In a patient with an intestinal fistula, Honigmann [213] demonstrated that considerable quantities of iron could be absorbed—of 0.4166 gm. of iron (in the form of ferrum citricum oxydatum) 0.3388 gm. or 81.33 per cent. were absorbed within two days.

The investigations of more recent years have been directed not only to metallic iron and the unstable combinations of the metal, but other substances which hold the iron in much stronger combination and which, partly from this peculiarity and partly from their chemic constitution, are closely related to the ferruginous nucleo-albumins, have also been proved to be capable of absorption. Such substances are hemol, hemogallol, carniferrin, and ferratin. After the correct experimental technic had once been determined (methods of Gottlieb, Kunkel, or Quincke) and the main question had been decided, it became of subsidiary importance whether this or that preparation is absorbed to a greater or less degree. At the present time mercantile considerations, rather than medical science, seem to arouse interest in the solution of this question.

At this point we will leave the iron question, but we will take it up again, in order to show its practical conclusions, when we come to consider the treatment of chlorosis.

THE CHARACTER OF THE URINE IN CHLOROSIS.

We can pass over a number of subjects relating to the urine, since they have been disposed of in some of the preceding sections. The excretion of nitrogen has been discussed. In the face of the results of the investigations upon metabolism no importance can be attached to the frequently quoted conclusion that "in chlorosis the excretion of nitrogen (urea) is diminished," since this conclusion was reached without control of the diet. The amount of urobilin (see p. 449) and the presence of the aromatic products of the decomposition of the albumins (see p. 422) have also been considered.

But little is known in reference to the individual nitrogenous substances and their combinations.

Urea.—Voges and Friedrichsen,[213a] in their investigations in the author's clinic, found that in chlorotics a strikingly large proportion of the total nitrogen was eliminated in the form of urea. Normally and with a mixed diet this proportion is 83 to 85 per cent. In 7 analyses the above-mentioned authors encountered these normal figures but twice; in the other cases the proportions varied between 87 and 93 per cent. P. Chatin,[214] who carried out similar experiments, also found the proportion of total nitrogen eliminated as urea to be between 83 and 86 per cent. in but 4 cases, while in 6 instances the values obtained were between 87 and 90 per cent. Since similar figures have also been determined in other diseases which do not resemble chlorosis, and since we have no clear insight into the cause of this phenomenon, we will limit ourselves to the statement of the fact. There are many objections to be urged against the conclusions of Chatin and Robin, that with a low percentage of total nitrogen eliminated as urea the oxidation in the body is diminished, and that with a high percentage the oxidation is increased. These objections are fully stated in the author's text-book upon the Pathology of Metabolism.

Ammonia.—In the cases of Voges and Friedrichsen, 4.9 to 8.1 per cent. of the nitrogen in the urine was combined as ammonia. This is a relatively large amount, since the normal figures are 2 to 5 per cent. when the individual is upon the same diet as that received by the above patients. The large amounts of ammonia serve as evidence of a more pronounced excretion of acids; the nature of the acids, in these cases, was not determined.

Uric Acid.—Voges and Friedrichsen found rather high relative values for uric acid. It constituted 1.2 to 3 per cent. of the total nitrogen, but these amounts are still within normal limits. In 6 patients the total amounts of uric acid excreted in the twenty-four hours were 0.51, 0.35, 0.50, 0.54, 0.81, 0.84, 0.39, 0.51, 0.75 gm.; the same amounts are also found in the twenty-four hours' urine of healthy women. After continuing our investigations for five days in the case of a young girl with severe chlorosis, we obtained a daily average of 0.65 gm. of uric acid per day (nitrogenous metabolism per day, 11 to 12 gm.; amount of urine, 2000 to 2400 c.c.; method of Ludwig-Salkowski). The figures from other sources are few in number. Bartels[215] found in one chlorotic girl 0.696 gm. of uric acid per day, in a second case, 0.2 to 0.4 gm. (method of Heintz). W. v. Moraczewski,[216] who determined

the amount of uric acid by Haycroft's method, records the following daily values:

Case	I.	0.11–0.68 gm. (twice, 2.552 and 3.201 gm.— ?)
"	II.	0.21–0.68 "
"	III.	0.12–0.54 "
"	IV.	0.40–0.69 "
"	V.	0.20–0.49 "
"	VI.	0.18–0.50 "
"	VII.	0.26–0.62 "
"	VIII.	0.25–0.63 "
"	IX.	0.42–0.64 "
"	X.	0.28–0.78 "
"	XI.	0.25–0.78 "

Creatinin.—But little is known in reference to the other nitrogenous components of the urine. K. B. Hofman[217] found 0.539 to 0.604 gm. of creatinin in the twenty-four hours' urine. These quantities are somewhat less than normal; this might have been dependent upon a limitation of the meats in the diet.

The Amount of Urine.—The statements in reference to the amount of urine are somewhat at variance. Some authors say that the amount is decreased, others designate it as normal, and a few have occasionally called attention to increased amounts of the excretion (Loock,[112] Bartels,[215] Rethers,[132] Luzet[1]).

Our own experience may be stated as follows: In uncomplicated cases, in which the amount of ingested fluid is left to the discretion of the patient, the amount of urine is at least normal; very frequently it is increased. The color of the urine is correspondingly pale and the specific gravity is low. Th. Rethers,[132] in his previously mentioned dissertation, published a large number of cases, in which polyuria was present. During the course of the disease, the daily excretion of urine is not uniform in amount. Disregarding temporary variations dependent upon changes of diet, a striking increase is often observed when the general condition commences to improve. In many chlorotics the amount of urine is relatively (or even absolutely) increased, when the amount of liquid ingested is diminished. This fact proves that superfluous water has collected in the tissues (see p. 402). In other chlorotics the amount remains normal or there are alternate periods of polyuria and of diminished urinary excretion. Only when complications were present have we seen a considerable and permanent decrease of the amount of urine (less than 1 L.), the specific gravity being high

and the urine concentrated. Such complications were edema, venous thrombosis with fever, and refusal of the patient to eat. The same observation was also made in a number of very severe cases of uncomplicated chlorosis. In 3 cases, every menstruation was accompanied by a decreased urinary excretion; after the menstrual flow had ceased, the amount of urine was correspondingly increased. The author has accurate notes in reference to 1 of these cases:

Before menstruation . . .	1400–1600 c.c.
During " . . .	500–750 "
On the following 5 days .	1500, 2550, 3200, 3800, 1800 c.c.

The amount then fell to 1300–1550, and remained at this point until the next menstruation, when it again fell to 600–800 c.c., and was again followed by a postmenstrual polyuria. No edema could be seen or felt during the course of the menstruation, but during the first menstruation the body-weight increased 2200 gm. and during the second 2450 gm. With the cessation of the menses and the appearance of the polyuria, the body-weight fell rapidly to its previous amount. During the entire nine weeks of observation the diet was uniform and the daily amount of ingested fluid varied between 1600 and 1800 c.c.

Of the clinical records at our disposal, we could utilize 159 for the construction of a small table. We have recorded those figures which most frequently recurred. Since it is not certain that the entire amount of urine was always obtained and measured, the figures must be taken to indicate only minimum values; the correct values are probably somewhat higher.

Daily amount of urine	less than 1000 c.c	in 15 cases	(9.4 per cent.).
" "	between 1000 and 1200 c.c.	" 42 "	(26.4 ").
" "	" 1200 " 1400 "	" 23 "	(14.5 ").
" "	" 1400 " 1600 "	" 9 "	(5.6 ").
" "	" 1600 " 1800 "	" 7 "	(4.4 ").
" "	" 1800 " 2000 "	" 18 "	(11.2 ").
" "	" 2000 " 2500 "	" 26 "	(16.3 ").
" "	" 2500 " 3000 "	" 11 "	(6.9 ").
" "	" 3000 " 3500 "	" 1 "	(0.6 ").
" "	" 3500 " 4000 "	" 4 "	(2.5 ").
" "	more than 4000 c.c.	" 3 "	(1.9 ").

Constituents of the Ash.—No investigations have as yet been made which allow of a determination of the variations in the amount of mineral substances. A. Robin [218] records a diminution of the phosphates, but no weight should be attached to such a statement, since nothing is said about the quantity of phosphates in the food ingested. W. v. Moraczewski [216] has recently studied this subject more accurately. He published the results of his examinations of the urines of 11 cases

of chlorosis, yet he says nothing of the quantity of food ingested and nothing of the amount of mineral substances contained therein. In spite of this, the author draws the following conclusions: 1. During the anemia, the excretion of the chlorids in the urine is diminished, but the excretion returns to the normal during the recovery from the disease. 2. The elimination of calcium phosphate is subject to the same variations as is the elimination of chlorin. 3. The alkaline phosphates are increased during the anemic period, but this increase disappears with recovery from the disease. We regret that we can not admit the correctness of these conclusions. A diminished elimination of chlorin and an increased elimination of phosphates, which Moraczewski designates as characteristic of chlorosis, can only be determined by accurate comparative observations of the diet upon the one hand and of the urine and feces upon the other. As soon as we deviate from this principle we open the door for endless speculation.

Albumin.—This is ordinarily found in chlorotic urine only in those traces which are common to all urines, and which are difficult of demonstration with the usual reagents (heat test, acetic acid and potassium ferrocyanid, potassiomercuric iodid).

Among chlorotics, however, there are always certain individuals whose urines constantly contain a certain amount of albumin. In 260 chlorotics this was observed 24 times (9.2 per cent.). If these figures are compared with those obtained by the study of albuminuria in healthy individuals (v. Leube, v. Noorden, Senator), it will be found that a slight albuminuria is certainly not more frequent, but rather more uncommon, in chlorotics than in the average healthy individual. The microscope fails to reveal any elements which might be referred to the kidney; usually the only find is a number of isolated hyaline casts such as are also present in the albuminuria of healthy individuals. The frequency of this slight albuminuria is by no means dependent upon the severity of the disease; the 24 cases above mentioned represented about an equal number of both the milder and more pronounced types of the affection. It is to be particularly emphasized that the albuminuria is also independent of the edema of the feet (see p. 402) and of the accumulation of water in the tissues (see p. 402). In these 24 cases of albuminuria, edema of the feet was present in but 2 instances. In 17 of the 24 patients the mild albuminuria persisted unchanged after recovery from the chlorosis.

In exceptional cases we encounter a special form of albuminuria which we must describe more in detail. Among the cases of "cyclic albuminuria," or of "intermittent albuminuria in young people," which

were first described simultaneously by Pavy [219] and the author,[220] there were also a number of chlorotics (see the collections of Heubner [221] and of Osswald [222]). The large amount of work that has been devoted to this subject in recent years has failed to find the cause of this albuminuria. The albuminuria is observed chiefly in half-grown boys and girls; it occurs only during certain hours of the day, in the morning, for example; at other times, particularly after prolonged physical rest, the urine is free from albumin. The remarkable observation is frequently made that the largest amount of the albumin is precipitated in the cold by the addition of acetic acid; this would indicate nucleo-albumin. Careful microscopic examination, even after centrifugation, usually demonstrates the absence of casts or other nephrogenic elements, although a hyaline cast may occasionally be observed. In the course of ten years we have encountered "cyclic albuminuria" in but 3 cases of chlorosis, although we have assiduously sought after new cases since our first publication. The excretion of albumin, which was limited to certain hours of the day, disappeared in two or three weeks, while the chlorosis was improving upon the administration of arsenic; no other therapeutic measures were adopted, but the rather emaciated patients were encouraged to indulge in a more liberal diet. In every case, the albuminous urine had a high specific gravity (1020–1025) and was highly colored; the non-albuminous urine was clear and abundant in quantity. In further accord with the previous descriptions, there was an entire absence of casts and of renal cells and a particular abundance of nucleo-albumin.

In 1 case the urine contained considerable quantities of other albuminous substances in addition to the nucleo-albumin; in the other 2 cases only traces were present. The first urine gave the following reactions: Acetic acid caused a dense clouding which increased upon prolonged standing; upon the following day the bottom of the beaker was covered with a thin layer of amorphous substances and of uric-acid crystals. The supernatant fluid was perfectly clear and was scarcely clouded by the addition of potassium ferrocyanid. The precipitate did not completely dissolve when treated with dilute hydrochloric acid and pepsin and placed in the incubating oven; the solution gave a beautiful biuret reaction, a marked precipitate with potassium ferrocyanid, and with other reagents for albumose. After the albuminuria had once disappeared it never returned, as was shown by frequent examinations of the urine, which, in 2 cases, were continued for months and years. All three girls made complete recoveries. The clinical symptoms were

such that no doubt could exist as to the correctness of the diagnosis of chlorosis.

With the exception of such infrequent cases, which may be easily recognized by their peculiarities, albuminuria is rare in uncomplicated cases of chlorosis. Diseases of the kidneys may simulate chlorosis upon superficial examination and are sometimes confounded with this affection (see "Diagnosis").

Sugar is never present in chlorotic urine. We have repeatedly tried to produce an alimentary glycosuria by the administration of 150 gm. (5 oz.) of grape sugar, but in only 1 instance have we obtained a positive result. Within three hours after the ingestion of the grape sugar, 0.7 gm. (10 gr.) of sugar appeared in the urine. In this case, however, the chlorosis was complicated with such pronounced symptoms of Basedow's disease, that it was doubtful whether the latter affection was not the main ailment of the patient. Chatin[214] also examined chlorotics for alimentary glycosuria; he never observed that sugar was eliminated in the urine.

The Toxicity of the Urine.—For the sake of completeness, brief mention will be made of the experiments which have been tried in chlorotic patients for the purpose of determining the toxicity of the urine. The investigators employed the method of Ch. Bouchard[223] and determined the so-called urotoxic coefficient. The method is as follows: As much of the twenty-four hours' urine of the patient is injected into the vein of the ear of a rabbit as is necessary to kill the animal. If we know the amount of urine necessary to kill the animal, the amount of the twenty-four hours' urine, the weight of the rabbit, and the weight of the patient, we calculate first how many cubic centimeters of urine would have been necessary to kill a rabbit weighing 1 kg. We then calculate from this how many kilograms of rabbit ("living material") the entire twenty-four hours' urine would have been able to kill. This number indicates how much poison is produced by the entire organism or by a certain number of kilograms of the human individual. We now divide the kilograms of rabbit, which the twenty-four hours' urine would have been able to kill, by the weight of the individual, and the result obtained is the "urotoxic coefficient." According to Bouchard, the average in health is 0.464. Picchini and Conti,[224] who deviated slightly from Bouchard's method, found that the urotoxic coefficient was larger at the height of the disease, and less after recovery. In opposition to this, P. Chatin[214] states that the production of poisonous substances in the body is diminished during chlorosis (diminution of the urotoxic coefficient). Chatin thinks that the Italian investigators

did not correctly interpret their results and that their figures, like his own, indicate a diminution in the production of poisonous substances in the body.

Four years ago[225] we first had the opportunity of critically studying Bouchard's method and, from then until the present, could never convince ourselves that the procedure fulfilled all the requirements of a scientific experiment.

THE TEMPERATURE OF THE BODY.

Chlorosis is generally considered to be an afebrile disease. While this is true in the great majority of cases we can not hold rigidly to this theoretic dogma. Disregarding febrile complications, every physician who regularly takes the temperature of his chlorotic will be able to record cases in which the temperature rose temporarily to ¼° to ½° C. (½°–1° F.), and sometimes still higher, above the normal.

One of the most careful observers of temperature in disease, C. A. Wunderlich,[226] first pointed out that chlorosis is occasionally accompanied by fever. H. Mollière,[227] Fr. Leclerc,[227] and Trazit,[228a] subsequently directed attention to the fever of chlorotics. Hayem[229] also increased the statistics by some valuable observations, and Eichhorst[1] frequently met with slight elevations of temperature (37.8–38.3° C. = 100–100.9° F.) without demonstrable cause. It goes without saying that all of these writers carefully excluded every complication which might have produced fever.

The most important question in practice is whether these cases of chlorosis which are combined with temporary or permanent elevations of temperature are not really concealed cases of tuberculosis (pulmonary or glandular). Our suspicions should always be directed toward this possibility, but it would be preposterous to look upon a simple elevation of temperature as an indication that the case was not one of pure chlorosis and that some complication, probably tuberculosis, was lurking in the background. The injection of tuberculin seems to us to be an important diagnostic aid in doubtful cases. We have frequently observed that chlorotics who had fever showed no further elevations of temperature after they had received 3 to 5 mg. of tuberculin. In such cases tuberculosis can be excluded with a fair degree of certainty.

We are ignorant of the manner of origin of the fever of chlorotics. It should be remembered that elevations of temperature also occur in all other diseases of the blood.

We are able to give the following small table from our statistics.

Only those cases are included which were examples of pure chlorosis. The temperatures were measured in the axilla:

In 140 cases of chlorosis there were such long-continued temperature records and such accurate clinical notes that all complicating causes of fever could be excluded. Of these 140 chlorotics

73	(52.1 per cent.)	had maximum temperature of	37.5° C.	(99.5° F.).
25	(17.8 ")	" " "	37.7° C.	(99.9° F.).
5	(3.6 ")	" " "	38.0° C.	(100.4° F.).
5	(3.6 ")	" " "	38.5° C.	(101.3° F.).
1	(0.7 ")	" " above	38.5° C.	(101.3° F.).

In most cases the slight elevations of temperature were only temporary and observed for but a few days; in the lesser number, they remained for longer periods of time.

A case which we observed in private practice is worthy of particular attention. It is not included in the above table:

The patient was a young girl, eighteen years of age, with the unmistakable signs of a severe chlorosis. The diagnosis was confirmed by the course of the disease, the patient completely recovering within six months. The temperature curve proceeded with the most remarkable variations. For periods of four or five days the temperature was decidedly febrile (rectal temperatures, morning 37.5–37.8° C. = 99.5–100.1° F.; evening 38.3–38.8° C. = 100.9–102° F.). Then would follow a period of from three to seven days, during which the temperature was normal. Such periods interchanged three times in succession and then the body temperature remained normal, while the general condition markedly improved. At the height of the disease the hemoglobin sank to 7 per cent. by weight, and the number of red blood-corpuscles was diminished to 3,800,000. The variations of temperature were not accompanied by any striking changes in the blood. The spleen was moderately enlarged. At the height of the disease the general physical condition seemed to be decidedly better during the febrile periods than in the intervening afebrile intervals.

This case recalls the temperature curves which have been occasionally observed in so-called pseudoleukemia and in pernicious anemia and which have been described as chronic relapsing fever (Ebstein,[230] v. Noorden [50]).

COMPLICATIONS.

Accidental Complications.—In the course of a disease, such as chlorosis, which has improvements, exacerbations, pauses, and relapses lasting for months and years, a great opportunity is given for complication with other diseases. Chlorosis even favors the simultaneous outbreak of other affections—this statement being particularly true of the acute infectious diseases. A still more striking fact is that chlorotics are greatly endangered by all infections. Typhoid fever, pneumonia, influenza, and scarlet fever are diseases which rarely give rise to much apprehension when they attack young and healthy individuals;

in chlorotics, however, the type of the disease is much more severe. The cerebral febrile symptoms are particularly marked and the patients soon pass into the stages of stupor and delirium. This is the cause of the well-known difficulty of nursing and feeding such patients; after a few febrile days, chlorotics are frequently in a condition of weakness that other patients would not have attained after a febrile period lasting two or three times as long. In acute articular rheumatism, to which chlorotics are decidedly predisposed, we have observed that endocarditis or pericarditis almost always makes its appearance and that an organic heart lesion remains behind in most cases. This recalls the statement of Virchow,[1] that grave diseases of the endocardium were rarely absent in cases of puerperal sepsis in chlorotics.

The acute and chronic infectious diseases, as well as the numerous organic affections, are only accidental complications of chlorosis. We would also include tuberculosis in this category, although some authors suppose that there is a more intimate connection between tuberculosis and chlorosis (see p. 405). Bright's disease is deserving of no more independent position, and it would only lead to confusion if we should assume the existence of an intimate relationship between the two diseases from a few common symptoms and recognize the mixed form which the French authors have described as "Chloro-Brightism." We have previously touched upon this question and will return to it again in the section upon Diagnosis.

There is also a series of diseases or of symptom-complexes which appear rather frequently in chlorosis, and which are so combined with the symptomatology of the disease that they can no longer be designated as purely accidental complications. In the previous sections this variety of complication has been sufficiently considered.

There are two affections which, to our minds, assume an intermediate position between the purely accidental complications and those which are immediately dependent upon the disease. These are gastric ulcer and Basedow's disease.

Gastric Ulcer.—The text-books have always pointed out the connection between the round gastric ulcer and chlorosis. Unfortunately, we possess no extensive statistics in reference to the simultaneous occurrence of the two diseases. We can not learn much from individual series of statistics from this and that clinic, since it is becoming more and more evident that gastric ulcer does not occur with uniform frequency in the different parts of the country and in the different classes of society. We might quote Luzet,[1] who expressly states that the frequent complication with gastric ulcer, reported by

German authors, is not observed in France. We were impressed with the rarity of gastric ulcer in the chlorotics treated at the Charité, in Berlin, after we had previously learned, as assistant in the Clinic at Giessen, to look upon gastric ulcer as a very frequent complication of chlorosis. Another condition making a critical decision difficult is the fact that the diagnosis of "gastric ulcer" is sometimes made quite arbitrarily. Many physicians are too quick to diagnose gastric ulcer; the natural result is that they frequently prescribe a series of dietetic regulations for their chlorotics with dyspeptic symptoms, and the patient is harmed more than she is helped. We would state our own experience as follows: Among the girls and young women who certainly have gastric ulcer there is always a relatively large number of chlorotics. When we reflect upon the enormous number of chlorotics, however, there are but few who simultaneously present absolute signs of gastric ulcer. In our last 35 cases of chlorosis, mostly of a severe type, we were able to diagnose a gastric ulcer definitely in but 1 instance; in a second case, the presence of a gastric ulcer could only be suspected with a fair degree of probability.

Many views have been expressed as to the causes which assist in the formation of a gastric ulcer in chlorosis. The greatest addition to our knowledge upon this subject was made by the brilliant experiments of Quincke[232] and of Dettwyler.[231] When they injured the gastric mucous membrane of animals, rapid repair was the usual result. If the animal was simultaneously made anemic by venesection, the reparative process was greatly delayed or entirely failed to make its appearance. If this knowledge is applied to the human individual we must assume that, with the existing anemia (or chlorosis), the gastric mucous membrane is more sensitive to deleterious thermal, mechanical, and chemic influences and is more easily injured by them than in health. If the injury has once taken place, the anemic quality of the blood interferes with repair and an ulcer results. This hypothesis is also supported by the observation of Riegel[233] and others, that both chlorosis and gastric ulcer are accompanied by hyperacidity of the gastric juice (see p. 418); the high degree of acidity constantly injures the base of the ulcer and delays repair.

If a gastric ulcer is present the treatment must, of course, be chiefly directed toward this affection. Rest in bed and the well-known restricted diet are indicated. Besides this the administration of iron should never be neglected, since the improvement of the chlorosis is of the most extreme importance for the rapid cure of the ulcer. Great caution must be observed in the administration of iron by mouth. If

the iron is given in greatly diluted solutions, we can not conceive why gastric ulcer should be regarded as a contra-indication to its administration. The much-feared corrosive action of iron is observed only with the solutions of more marked concentration. In such cases we prefer dilute solutions of ferric chlorid. If the dilute solutions of the iron salt should not be well borne, the only thing left is the subcutaneous injection of citrate of iron, according to the suggestion of Quincke.

Basedow's Disease.—The relations between chlorosis and Basedow's disease are most remarkable and still unexplained. It has long been known that a completely developed Basedow's disease or some of its well-known features are of frequent occurrence in chlorosis. This was energetically pointed out by Wunderlich.[234] In Germany this connection was later called in question and the association of the two diseases was regarded more as an accidental occurrence. Such were the views expressed by Eulenburg[235] and Immermann.[1] The French held much more rigidly to the teaching that chlorosis, to a certain extent, assisted in the production of Basedow's disease (Teissier,[236] Hayem,[1] Luzet[1]). Chvostek[185] has recently directed attention to this point in a most meritorious manner. He described several cases of chlorosis which were associated with distinct symptoms of Basedow's disease. On the whole, the publications are scanty and rather uncertain.

It is far from our thoughts to claim that there is an intimate relation between the two diseases, and all the more so, because we are decidedly of the opinion that Basedow's disease is a peculiar anomaly of metabolism dependent upon disease of the thyroid gland, while we would trace the origin of chlorosis to other organs (sexual apparatus and bone-marrow). Both of these affections are diseases of metabolism, quite different in their nature, which are frequently found associated with each other, just as gout and diabetes, or diabetes and pathologic obesity are often observed in the same individual.

In chlorotics the most frequent symptoms of Basedow's disease are enlargement of the thyroid gland (the "struma chlorotica" of some authors), a permanent increase of the pulse-rate, hyperhidrosis, and tremor. Exophthalmos is more rare, although it is occasionally observed.

In the following statistics we have omitted those cases in which only one of the above-mentioned symptoms was present. Of 255 cases of chlorosis

7 cases had enlargement of the thyroid gland, exophthalmos, accelerated heart action, tremor, hyperhidrosis, and muscular unrest.

4 cases had enlargement of the thyroid gland, tachycardia, tremor, and hyperhidrosis.
7 cases had tachycardia, tremor, and hyperhidrosis.
5 " tachycardia and tremor.
3 " tachycardia and hyperhidrosis.
3 " enlargement of the thyroid gland and tachycardia.
5 " a vascular enlargement of the thyroid gland without concomitant symptoms.

Of the 255 cases it will be seen that there were 34 which presented symptoms of Basedow's disease. These symptoms sometimes persisted after the disappearance of the chlorosis and sometimes they were distinctly developed only at the height of the disease.

We must record 1 case in particular. It was one of the rarest clinical occurrences that we have ever encountered:

The patient was a girl, twenty-two years of age. She said she had suffered repeatedly from chlorosis, and that during one of the previous attacks her neck had become larger in circumference. When we first saw the patient she had a severe type of pure chlorosis, which, according to her statements, had reached its maximum development in ten to fourteen days. In addition to the marked paleness of the blood and of the skin there was such an extreme degree of muscular weakness that the patient was confined to bed. The neck was 34 cm. in circumference; there was not the slightest indication of an enlargement of the thyroid gland. Two days later, the neck was 38 cm. in circumference, the pulse-rate had increased from 80 to 106, and the eyeballs were distinctly protuberant. In the two succeeding days the circumference of the neck increased to 39½ cm., there was a markedly palpable and pulsating enlargement of the thyroid gland, vascular murmurs could be heard over the thyroid, the exophthalmos became more marked, and there was permanent hyperhidrosis, sleeplessness, and extreme weakness. This was the acme of the disease. Upon the following day all the phenomena commenced to disappear, and after five more days the patient showed no indication of having passed through an acute attack of Basedow's disease. The circumference of the neck returned to 34½ cm. and the pulse-rate sank to 74. From the first day of observation (and, consequently, before the appearance of the symptoms of Basedow's disease) the treatment had consisted of the administration of iron and arsenic.

If Basedow's disease is associated with chlorosis, the therapeutic measures to be recommended are the greatest possible mental rest, the avoidance of physical exertion, an abundant diet, and the employment of arsenic, with or without the simultaneous administration of iron.

COURSE AND PROGNOSIS.

In reference to the course of the disease we may differentiate the following groups:

Simple Chlorosis.—Ordinary chlorosis appears in a series of attacks. It develops more or less rapidly—*i. e.*, in a few days or weeks—until it reaches a certain acme, where it remains for a longer or shorter period of time, frequently exhibiting slight variations for the better or for the worse, and then gradually disappears. The entire attack usually lasts for from two to four months. Complete recovery is rarely attained upon the subsidence of the actual attack, and the blood but rarely returns quickly to assume its normal composition. As a rule, slight disturbances of the general health, pallor, retardation or irregularity of the menses, and incomplete regeneration of the blood are present for quite a time as evidence of the past disease. Recovery finally occurs after the lapse of six months or of a somewhat longer period. The disappearance of the disease may be permanent, but in the majority of cases recurrences are observed, which may be repeated for a number of years. It has been observed that certain individuals are always reattacked by chlorosis at definite seasons of the year, and such cases are known as winter chlorosis, spring chlorosis, etc., as the case may be. According to O. Rosenbach,[1] late summer chlorosis is said to be the most frequent form. This is an experience that we can not confirm; in our patients with annual attacks of chlorosis the majority were affected during the spring.

The development of the disease may be characterized by longer periods of time between the successive attacks. This is particularly the case in strong young girls who are well nourished; it is more frequently encountered in the higher classes of society than among the working population, and is more common in individuals who are attacked relatively late in life (seventeen to nineteen) than in very young girls. The prognosis is decidedly favorable. A certain tendency to recurrence persists until maturer years, sometimes extending into the fourth decennium, particularly in unmarried and in childless women. In this form of chlorosis, pregnancy has an opposing influence to the recurrences of the

disease. The tendency to recurrence finally disappears without leaving behind any permanent damage from the past disease.

The great majority of the cases of chlorosis pursue the course which has just been described.

Chronic Chlorosis.—Under this head are included those cases which last for a number of years, sometimes ten or twenty. In the protracted course of the disease there are improvements and exacerbations, but the patients are always pale, and the hemoglobin of the blood is diminished. In these cases there is always a simultaneous diminution of the number of the red blood-corpuscles. The patients always present symptoms, particularly disturbances of menstruation, some variety of dyspeptic phenomena, muscular weakness, and fatigue upon slight exertion. In time the general nutrition almost always suffers, the resistance of the nervous system is diminished, and hysteria and neurasthenia find an excellent basis for their development.

Chronic chlorosis is also characterized by the occurrence of distinct attacks, inasmuch as the periods of improvement and of exacerbation alternate with each other independently of any form of treatment. Since the disease does not completely disappear, in spite of the best care and treatment, it is to be supposed that this type is due to a permanent, or to a gradually disappearing, disturbance of function. It can be scarcely anything else than a condition of atony of the hematopoietic organs. The cause of this atony can not always be established; sometimes, probably in the majority of cases, it depends upon an aplasia, comparable to other instances of retarded development (dwarfs, deficient development of the bones, of the vascular apparatus, of the breasts, or of the genitalia), which may occur separately or combined with the chronic form of chlorosis, and which probably provide the basis for the development of the disease (vascular anomalies, anomalies of the sexual organs). In other cases with well-developed organs, deleterious influences, such as unfavorable nutritive conditions or latent tuberculosis, may permanently affect the function of blood-formation. We do not consider it advisable to designate such cases as chlorosis.

The chronic form of chlorosis begins very early in the first half of the second decennium, or it may even date back to the years of childhood; in rare instances the disease may not appear until the eighteenth year or even later. These individuals are usually weakly and also present other signs of retarded development (a small or slender body, a delicate osseous system, scanty musculature, deficient panniculus adiposus, hypoplastic mammary glands, deficiencies of the internal genitalia).

Sometimes one, and sometimes several, of these signs of degeneration may be present. This type of the disease rarely affects those of strong and well-developed physique.

The termination of these cases varies greatly. Complete recovery frequently occurs after the chlorosis has existed for years. This shows that a congenital or acquired insufficiency of the hematopoietic organs may be overcome by subsequent maturation. In this respect the treatment is of great importance. In some cases the favorable influence of married life is unmistakable; in other instances the chlorosis disappears, but is particularly likely to return during pregnancy or the puerperium. Recovery does not always take place. Many women remain more or less chlorotic all their lives or, at least, until the menopause. Without ever being dangerously ill, they always suffer from some of the symptoms which are common in the chlorosis of youth. The cardinal symptom of the chlorosis of younger years, the pallor of the skin, gradually disappears with advancing age, since the capillaries dilate and marked pigmentations make their appearance. This peculiarity of old cases often causes us to forget the possibility of the presence of chlorosis. If the anemnesis is carefully elicited, however, the symptoms present may be traced directly to an undoubted chlorosis of youth; the examination of the blood regularly reveals a marked decreas of hemoglobin, which sharply contrasts with the appearance of the patient.

The prognosis of these forms of chlorosis, which are chronic from their first appearance, is subject to great variation. They frequently end in recovery, but even these favorable cases may furnish cause for alarm. If the blood is watery and poor in hemoglobin at the time of the most rapid development of body and mind, the resistance of the organism later in life must be impaired. Deficient physical development, impairment of physical and mental energy, a badly trained will and reason, deficient education, and capriciousness are frequently the results of long-continued chlorosis and of the enforced idleness of the body and of the mind, which the disease imposes upon its victims.

It must also be remembered that chlorosis, particularly the chronic form, cultivates the ground for the development of other diseases, and delays the convalescence of intercurrent affections. In chronic chlorosis it should also be borne in mind that the case may not be one of pure chlorosis—*i. e.*, a disturbance which is limited to deficient blood-formation. Other grave developmental disturbances may also be present, such as hypoplasia of the vascular system with the danger of subsequent cardiac weakness, hypoplasia or functional disability of the genitalia

with the danger of permanent sterility; or the chronic anemia may only simulate chlorosis and actually be due to a latent tuberculosis.

Chlorosis with Complications.—Chlorosis favors the development of certain other diseases, some of which are dangerous and even fatal. Two such complications are gastric ulcer and thrombosis. Together with trauma and intoxications, they constitute, by far, the most frequent causes of death in chlorotic girls and women. All other complications intimately connected with chlorosis are not dangerous to life, but they may render the disease more serious and delay recovery.

DIAGNOSIS.

CHLOROSIS does not belong to the diseases with pathognomonic symptoms. Every individual symptom is observed in other diseases, particularly in the remaining forms of anemia and, on the other hand, with the exception of the impoverishment of the hemoglobin of the blood—which is common to all anemias—there is no symptom which can not be wanting in the individual case without affecting the diagnosis. The diagnosis must not be based upon individual symptoms, but upon the entire clinical picture and upon the exclusion of other diseases. The diagnostic features are consequently partly of a positive and partly of a negative character.

POSITIVE DIAGNOSTIC FEATURES.

The Anemic Condition of the Blood.—A diminution of the amount of hemoglobin in the blood is the foundation upon which the diagnosis is based. A patient who is apparently anemic and yet whose blood contains a normal percentage of hemoglobin may be designated as anemic or as oligemic, but never as chlorotic. On the other hand, it can not be maintained that in chlorosis only the hemoglobin is diminished and not the number of red blood-corpuscles. As a rule, the hemoglobin impoverishment is greater than the decrease in the number of red cells; if the opposite condition obtains, it is evidence against the existence of chlorosis. The normal or approximately normal condition of the leukocytes is also to be emphasized.

The Female Sex.—While we do not deny the possibility of the development of anemic conditions and their sequelæ in the male sex, particularly in the young, which may be dependent upon the same disturbances of the hematopoietic function, as is chlorosis, we do not believe that the occurrence of such a condition has been definitely proved. Until we are fully cognizant of all the causes for the development of the disease, the word "chlorosis" should be reserved for the female sex (see pages 341, 342, and 347).

The Youthful Age of the Patient.—Great weight is to be laid upon this point. The anemias of childhood (until about the twelfth year) can but rarely be designated as true chlorosis. Considerable hesi-

tation should also be exercised in diagnosing as chlorosis those anemias which develop in the second half of the third decennium in individuals who have never been chlorotic. Nevertheless, advanced age does not exclude chlorosis, particularly if the anamnesis reveals the previous existence of attacks of chlorosis or if the chlorosis has been present as a chronic condition since the age of puberty. In elderly women and in girls a careless diagnosis of chlorosis is made much too frequently and with the greatest detriment to the patients. Not only should other causes of anemia be excluded, but the diagnosis should be confirmed by an examination of the blood. There are quite a number of women who apparently have chlorosis and who present many features of the disease, yet their blood is rich in hemoglobin and in red blood-corpuscles. The discovery of such a condition of affairs would at once exclude the presence of chlorosis.

Deficient Development of the Sexual Organs.—Although true chlorosis occurs in individuals with perfectly developed organs of generation, it is, nevertheless, an established fact that a deficient development of these organs, together with the so-called signs of degeneration in some portion of the sexual apparatus, are much more frequently found in chlorotics than in other women. Whether this hypoplasia is to be regarded as the direct or indirect cause of the chlorosis, the existence of the anomaly is, nevertheless, a point in favor of the diagnosis.

Marked and Rapid Improvement upon the Administration of Iron.—The curative action of iron is also observed in other forms of anemia, but never so distinctly as in chlorosis. If, however, the case does not improve when placed upon iron, it is not to be supposed that chlorosis is not present.

The Rapid Development of Anemia by a Series of Attacks.—This is indicative of chlorosis, if no other disease, particularly the losses of large amounts of blood, can be made responsible for the anemia. This peculiarity of chlorosis is very important from a diagnostic standpoint. In chronic anemias of uniform intensity, which last for years, great caution must always be observed in designating the case as one of chlorosis.

The General Condition of the Patient.—Of the long list of symptoms and signs peculiar to chlorosis, a certain number are always absent in the individual case. No two cases of chlorosis are absolutely alike: in one case, one set of symptoms predominate, while in another an entirely different train of disturbances is observed. The entire symptom-complex, and the appearance, course, and disappearance of the disease are, however, highly characteristic and of more diagnostic

significance to the experienced physician than the most careful analysis of the individual symptoms.

NEGATIVE DIAGNOSTIC FEATURES.

Since practically all of the symptoms of chlorosis are found in other forms of anemia it is of considerable importance, in every case, to exclude the presence of other diseases of the blood. An examination of the blood will exclude some of these affections, such as both forms of leukemia, severe cases of so-called pernicious anemia, and the cases of secondary anemia, which are accompanied by extreme leukocytosis. Other forms of anemia, which are sharply differentiated from chlorosis by their etiology, may produce a clinical picture and a condition of the blood which resembles true chlorosis. The affections to which the attention of the diagnostician is to be directed may be best indicated by a consideration of those diseases with which chlorosis is most frequently confused in practice.

Intestinal Parasites.—It has long been known that *Ankylostomum duodenale* and *Bothriocephalus latus* can produce anemia. In regions where these parasites are common they are rarely overlooked; elsewhere they are likely to give rise to confusion. Up to the present time we, personally, have treated only 2 cases of bothriocephalus anemia. In both instances the patients were young girls who had been regarded as chlorotics for a long time. The expulsion of the worm was followed by rapid recovery. Opinions vary in reference to *Tænia mediocanellata* and *Tænia solium*—the latter worm scarcely ever occurring in Germany at the present time. In the majority of cases, according to our experience, these worms do not cause a trace of anemia. In children and in young girls who are predisposed to anemia, however, they are not rarely the determining causes of an impoverishment of the blood. If this were not the case it would be hard to understand the rapid recovery from the anemia after the expulsion of the parasite. We have seen several such cures in cases which previously had been unsuccessfully treated with iron for long periods of time. The same statements are true of *Ascaris lumbricoides.* From these facts it will be seen that in every case of anemia the evacuations of the patient should be examined microscopically for the presence of the eggs of parasites, although the diagnosis be ever so well founded. In obstinate cases of anemia such an examination is of particular importance.

Tuberculosis.—Incipient tuberculosis frequently produces an anemic condition that strongly resembles chlorosis. It is not always possible to differentiate the two affections from their symptomatology

and from the condition of the blood. The similarity may extend even further, since, in both cases, the cause of the anemia, or the changed relations of the processes of blood-formation and of blood-destruction, may be identical. Their etiology, however, is different and the proper diagnosis of the condition is consequently of the greatest importance. It is possible that a girl with old or recent tubercular foci in her lymphatic glands or lungs can also develop a true chlorosis, but it is more cautious from a prognostic and therapeutic standpoint to exclude this possibility and to regard tuberculosis when present as the cause of the anemia in every case. Tuberculosis may be recognized in its early stages by a careful consideration of the anamnesis and by frequently repeated examinations of the lymphatic system and of the lungs. Temperature records are of but relatively small assistance; their importance for the differential diagnosis between chlorosis and the early stages of tuberculosis has been greatly overestimated. Tuberculosis sometimes makes its appearance unattended by fever, and long-continued measurements of the temperature several times every day may consequently reveal nothing abnormal. Upon the other hand, temperatures of 38.5 C. (101.3 F.) and higher are occasionally observed in cases which subsequently prove to be undoubted chlorosis. In these cases the reaction of the body to tuberculin seems to us to be of the greatest importance. We always employ it in doubtful cases and are very well pleased with the diagnostic aid furnished by the procedure. The habitual temperature curve of the patient is first ascertained by repeated measurements of the temperature at stated intervals for several days. One mg. of tuberculin is then injected, preferably late in the evening; if there is no abnormal rise of temperature upon the following morning or afternoon, 3 mg. should be injected, and this is to be followed with 5 mg. upon the succeeding day if the result is still negative. Fever after the injection definitely indicates the presence of tuberculosis; if the temperature remains normal, the absence of tuberculosis is almost as positively indicated. In our opinion, there are no other conditions in which the results of the injection of tuberculin are so significant and decisive as in chlorosis and tuberculosis (see p. 460).

The Simple Anemias.—These are due to unhealthy modes of life, to damp lodgings, to deficient light, air, and exercise, to inappropriate diet, to lack of sleep, and to an overburdening of the youthful organism with mental or physical work. These deleterious influences will produce anemia in all individuals, whether they are young or old, male or female; they are evidently instrumental in paralyzing the hematopoietic organs and in preventing a healthy formation of blood.

We are still ignorant of the portion of the organism first attacked and of the method of operation of these injurious influences. The blood, particularly in elderly individuals, frequently assumes characteristics which differentiate it from that of true chlorosis. The hemoglobin impoverishment is but slightly, if at all, more marked than the decrease in the number of cells, and the serum usually loses in density and albumin percentage. There are but few whose blood examinations are accurate enough to form the basis of a differential diagnosis. Even when these results are accurate they are not to be depended upon, since it is only the extremes that are characteristic. The extremes, however, may be recognized without such complicated diagnostic accessories and the analysis of the blood rarely allows of positive conclusions when the clinical diagnosis is in doubt. The conditions are still more complicated by the fact that all those deleterious influences which cause simple anemia in other individuals may produce a true chlorosis in those who are predisposed by age and sex, which loses more or less of its reaction to the exciting cause and continues to exist as an independent affection. This gives rise to new difficulties in the critical study of anemic conditions in girls and women, and we are confronted by the question, "Where does simple anemia cease and where does chlorosis begin as an independent disease?" The practical difficulties are by no means so great as are the theoretic ones. If a careful study of the mode of life reveals gross examples of some of the previously mentioned deleterious influences, it is always advisable to designate them as the most likely cause of the anemia and to refrain temporarily from diagnosing the case as a chlorosis which has become independent of the exciting cause. This is of therapeutic importance, since it would be a grave error to attempt to cure such a case by the administration of iron when good beefsteak, sufficient rest, and healthier lodgings are indicated.

Anemia from Hemorrhage.—Almost the only hemorrhages to be considered under this head are the hematemeses of gastric ulcer; hemorrhages from the intestine are of rarer occurrence. All other hemorrhages excite such attention that they are sufficiently appreciated by both the physician and the patient. This is not so with the hemorrhages occurring in the upper portion of the gastro-intestinal canal. Gastric or duodenal ulcer often produces no symptoms or there are no greater disturbances present than in the majority of cases of chlorosis. The escaping blood becomes so changed in its long course from the stomach to the rectum that it is difficult for the laity to recognize it as such. If the evacuations are not carefully and repeatedly examined many an ulcer will be overlooked, and the case regarded as one of

chlorosis, to the great detriment of the patient. The most careful examination of the blood will not save the diagnostician from this error, since the more important characteristics of chlorotic blood and of the blood after hemorrhage are identical. It may not be amiss to emphasize the fact, that a physician who overlooks bloody stools in a young girl and treats the disease as chlorosis, could be accused of malpractice.

Diseases of the Kidneys.—Chronic nephritis always leads to anemia, particularly in youthful individuals. In certain forms and stages of the disease, the patient acquires that puffy appearance and that alabaster transparency of the skin which is also observed in chlorosis. Chronic nephritis may also be accompanied by headache, palpitation, digestive disturbances, and a sensation of weakness, so that confusion frequently follows a superficial examination if the urine is neglected. The omission of the examination of the urine is to be considered as evidence of gross negligence on the part of the physician. There is not only a large percentage of albumin in the urine of these cases of nephritis in youthful individuals, but the blood is also characterized by certain peculiarities. In nephritis the specific gravity and the dry residue of the serum are usually diminished, while in chlorosis this is not observed, or at least only to an insignificant extent.

Certain French authors, following in the lead of Dieulafoy,[237] have recently attempted to differentiate a special form of chlorosis which is associated with chronic albuminuria or Bright's disease. In the literature this affection is known as "chloro-Brightism" and has been made the subject of dissertations by Chatin,[214] Labadie-Lagrave,[238] and Duco.[239] The cases of sudden fatal pulmonary edema in anemic girls described by Hanot[240] and Vincenti[241] also belong under this heading. The separation of these cases has no justification and can only result in confusion. They are cases of true nephritis which produce marked anemia and its consequent sequelæ. In such patients the well-known symptoms of chlorosis dominate the clinical picture, as they always do when anemic conditions develop in young girls.

Beginning Cerebral Diseases.—In youthful individuals these affections rapidly produce anemia, and many an apparent case of chlorosis with dizziness, attacks of unconsciousness, nausea, exhaustion and pallor has subsequently proved to be a brain tumor or a basal meningitis.

Beginning Pregnancy in Unmarried Girls.—The usual molimina of a beginning pregnancy are associated with those evidences of mental worry which naturally arise under such conditions. The

general nutrition suffers greatly and so does the quality of the blood. Young girls who were previously in blooming health rapidly lose weight and exhibit those manifold disturbances which are also observed in true chlorosis. For a long time such cases are regarded as chlorosis by the family and friends of the patient. It is the duty of the physician to gain the confidence of his patient sufficiently to allow him to determine the true state of affairs.

Congenital Hypoplasia of the Vascular System.—The development by a series of attacks, the rapid appearance and disappearance of the symptoms and of the anemia, and the possibility of cure, all speak decidedly against the teaching that vascular hypoplasia is the anatomic foundation of chlorosis. We believe that this statement expresses the position held by the majority of clinicians at the present day. Thanks to the classic descriptions of O. Fräntzel, pronounced cases of congenital hypoplasia of the vascular system with consecutive cardiac hypertrophy and subsequent cardiac weakness, with a tendency to stasis and endocarditis, and with the frequent association of deficient development of the entire body, produce such a characteristic clinical picture that the diagnosis is scarcely ever mistaken at the present day. This condition is also unlikely to give rise to confusion when a *marked* anemia is present as a secondary phenomenon. The study of Virchow's celebrated dissertation teaches that his descriptions were based *upon* such cases—cases that no clinician of the present day would allow to go to the postmortem table with the diagnosis of chlorosis.

Nevertheless, the diagnosis "hypoplasia of the vascular system" is not incompatible with the diagnosis "chlorosis," since this anomaly may play an important rôle in the etiology of the affection which we designate as chlorosis from a purely clinical standpoint. We recognize, with Virchow, that hypoplasia of the vascular system favors a deficiency of blood-formation. When hypoplasia of the vascular apparatus is present in an individual at the age of puberty, and this *individual* becomes subjected to external deleterious influences, anemia is not slow in making its appearance and the well-known symptoms of chlorosis and their sequelæ become manifest, as is usually the case when young girls become anemic. According to our conception, hypoplasia of the vascular system is a favorable basis for the development of chlorosis and may also delay convalescence and favor the subsequent recurrence of the disease. From a prognostic and therapeutic standpoint, it is important to recognize or exclude, at the earliest possible moment, the coöperation of this factor in the origin of every case of chlorosis. The art of diagnosis, however, is frequently unable to lead to a decision upon this

point, since the milder degrees of hypoplasia of the vascular system are difficult of recognition. The long duration of the disease, the resistance to reasonable treatment, and the more marked predominance of the cardiac symptoms, frequently furnish some aid to the diagnosis. These features are not characteristic, however, since chlorosis can persist for a long time when the vessels are normal and, on the other hand, cardiac and pulmonary symptoms are also peculiar to some cases of chlorosis which soon recover, leaving the patient in perfect health and with a normal heart.

TREATMENT.

PROPHYLAXIS.

Is it possible to prevent chlorosis? In a certain number of cases this question is to be answered in the affirmative, while in other instances it must certainly be denied. Even in the latter cases, however, much may be done to ameliorate the course of the disease.

We will start with the well-grounded supposition that the foundation of numerous cases of chlorosis exists early in life in the form of acquired or congenital weakness of the hematopoietic organs. The individual is consequently predisposed to the development of the anemias in general, but for the appearance of the particular form of anemia known as "chlorosis," an anomaly of the genital gland which leads to the abolition or impairment of a definite function ("internal secretion") must also be present. This anomaly occurring within the sexual apparatus must also be traced to a congenital predisposition.

Since the functional weakness of both systems is dependent upon congenital influences and represents a true anomaly of development (anatomic hypoplasia), the treatment is rather hopeless. Even the best hygiene of body and mind and the most appropriate diet are powerless when confronted with anatomic anomalies of development which were present in the embryo. There will, consequently, always be cases which make their appearance in spite of all preventive measures. In other cases, however, in which the congenital functional weakness is not so well marked, or where it develops later in life, there is some hope of overcoming this anomaly and preventing chlorosis by a proper regulation of the mode of life.

The prophylactic treatment practically includes all those measures which are necessary to strengthen the organism in childhood and in the early years of maturity. Particular attention must also be given to those measures which have a known or probable influence upon blood-formation. If we succeed in strengthening the body in childhood and in maintaining this condition, the danger of the appearance of chlorosis at a critical period is greatly diminished. Even should the individual be attacked, the disease will probably pursue a milder course, since,

with certain exceptions, experience teaches that strong persons recover from chlorosis much more quickly than weakly individuals.

This is not the place to enter into a general discussion as to the proper care and nourishment of children which are necessary to produce an organism capable of resistance. We will consider only as much of this subject as has a bearing upon chlorosis.

NUTRITION.

The diet should be sufficient to produce and maintain "good general nutrition." Everyone knows what is to be understood by this term. In growing girls it signifies a strong musculature and a well-developed panniculus adiposus. In young girls beyond the tenth year the layer of subcutaneous fat should be considerably better developed than in boys of the same age. An amount of fat that is sufficient for a boy might be frequently designated as scanty for a girl of the same age. On the other hand, we are not supposed to produce a condition of obesity.

The diet has relatively little influence upon musculature. If the diet is not absolutely niggardly, the muscles will develop according to the demands made upon them and according to their hereditary disposition. The richest diet remains permanently ineffective if the other factors favoring muscle-growth are absent. On the contrary, the diet is of decided importance for the deposition of the subcutaneous fat. It is a great error to lay little weight upon the regular cultivation of this fat, for, although this tissue has no independent life and represents only reserve material, it is constantly observed that individuals with normally developed fatty tissue are more capable of resistance than lean individuals. The latter statement is particularly true of children, and experience shows that in these individuals a normal amount of fat practically means a strong constitution in general. I do not refer to instances of pathologic obesity or to those increased amounts of adipose tissue which are obtained by temporary overfeeding. In childhood, however, these conditions tend to be of short duration. The temporary results of overfeeding are not to be considered; they frequently do more harm than good. It is much more prudent to favor the gradual deposition of fat and then to maintain what has been gained.

The Supply of Fats.—If the ordinary diet is not capable of producing a sufficient amount of subcutaneous adipose tissue in children and in young girls, we should advise the employment of the fats themselves for this purpose. The desired result can not be obtained with

carbohydrates, since these individuals usually have small appetites. The diet usually consists of a relatively large amount of these substances, and they would have to be increased to such an extent that there would be a constant struggle between physician and patient, which would usually terminate in the defeat of the physician. On the contrary, the amount of fat in the diet of children is usually less than it should be, and can easily be augmented without causing much of an increase in the total amount of food. Much depends upon the nature of this fat. In youthful individuals, fat meat and bacon are not to be recommended, since they soon excite the disgust of the patient. The fat, particularly in the form of butter, should be generously mixed with the vegetables and farinaceous foods, and the individual should also be encouraged to consume considerable quantities of butter with bread and potatoes. It is highly advantageous to add cream to the milk, and to administer some of the so-called medicinal fats. We have entirely abandoned the use of cod-liver oil and now employ oleum sesami [242] exclusively. Other methods of forming fat, such as the administration of alcohol and physical rest, are not to be considered in reference to children.

The Supply of Albumins.—In addition to the special purpose of forming fat, the diet of children and of youthful individuals must contain a generous quantity of albumin, if they are to be made strong and capable of resistance. Children should receive more albumin in proportion to their body-weight than is required by adults. This requirement is nearly always complied with, unless the parents are very poor, and it is only in rare instances that the physician finds it necessary to increase this article of diet.

Vegetables and Fruits.—The necessity of a generous supply of vegetables and fruits must be particularly emphasized. In Germany, at least, and particularly during the winter, these articles are not sufficiently represented in the diet of children. They are of the greatest importance for the normal development of the body and of all of its functions. As far as children are concerned, we believe we could do better by following the dictates of the most rigid vegetarianism than by feeding the children as though they were carnivora, according to the bad custom which is still quite prevalent. At this place, it is particularly appropriate to emphasize sharply the importance of green vegetables, since we are practically dependent upon the vegetable kingdom for the greater portion of the iron which is necessary for blood-formation (see p. 451). The iron occurs in vegetables in the form of highly constituted ferruginous nucleo-albumins (Bunge [1]). Although other combinations of iron (iron salts, organic preparations of iron of

simple molecular construction) may likewise be employed in blood-formation, they are never utilized by healthy individuals, who procure their entire supply from the nucleo-albumins. If we limit the most important sources of iron—the vegetables and the fruits—we cause a certain sluggishness of blood-formation and an entire lack of reserve iron, such as is normally found in the liver, spleen, and bone-marrow of healthy, well-nourished individuals. From the inappropriate selection of foods such persons acquire a predisposition to chlorosis.

EXERCISE. FRESH AIR. BATHS.

In young girls with a delicate constitution or a family history that makes us fear the development of chlorosis, we should pay special attention to those accessory measures which bring the patient in the fresh air, favoring the development of the muscles and the strengthening of the body. Experience shows that these factors are powerful stimuli to blood-formation. They are to be employed before the outbreak of the chlorosis, and also in girls who have been chlorotic, to avoid a recurrence of the disease. These measures are intended to spur the patient on to increased exertion by stimulating the physiologic process of blood-formation and, in this manner, to overcome the congenital or acquired weakness of the hematopoietic apparatus. The nature and the extent of the physical exercise which is to be prescribed for growing girls is so dependent upon the individual environment that we can not discuss it in detail. Children who grow up in large cities should spend their vacations in the country. The selection of the particular locality will depend upon circumstances; it is by no means necessary that the individual should be sent to a celebrated bathing or mountain resort. If the living apartments are suitable, any country place with wooded surroundings will usually be all that is required. Those places are to be preferred which are in the vicinity of lakes affording bathing facilities, and also those which are situated in mountainous districts. There is likewise no objection to high mountainous resorts. The old prejudiced view that children bear considerable elevations badly (such as the Engadine, for example) has been practically disproved. A high altitude is, if anything, a powerful stimulus to blood-formation and aids in the exercise and strengthening of the hematopoietic organs. Experience shows that the same may be said of a sojourn at the seacoast and of the use of brine baths. We must not consider these things from the standpoint of the laboratory and say, "Experiment has not proved the influence of these factors upon blood-formation, and consequently it does not exist." Practical experience is the only safe guide, and it presents

evidence of an unmistakable character. We would also mention that in 1888 we estimated the hemoglobin in a large number of children, before and after their summer vacation, at Nauheim; the hemoglobin was increased in every case, sometimes to quite a marked extent. Unfortunately, we are unable to find the records of these percentages. In practice, those children who seem particularly to need strengthening and stimulation of hematopoiesis should be annually sent to a high altitude, to the sea, or to a locality where brine baths may be obtained. Those high altitudes which also have bathing facilities are to be particularly recommended. To attain the desired result, as much stress is to be placed upon bathing as upon muscular exercise. These baths should be employed not only during the brief summer outing, but also in everyday life. Ordinary baths, their temperature not exceeding 90.5° F., with a subsequent cool douche or shower, may be employed; river baths, swimming baths, and sponge baths are also to be recommended. The physician should be warned against condemning weakly individuals to heroic cold-water cures. The result obtained will be in direct opposition to the effect desired.

MENTAL WORK AND THE INFLUENCE OF THE MIND.

It is one of the features of the present day to impose a large amount of study and the acquirement of a broader education upon young girls, that they may be better fitted to acquire independent positions for themselves in the battle for existence. As men we can think what we will of the "new woman"; but as physicians it is our duty to oppose their advanced theories. No one will deny that the physical and mental growth of many girls is quite sufficient to stand the fatigue and exertion which the higher education and the learned professions have always been accustomed to place upon the growing youths of the male sex. In the enormous majority of young girls this is not so. We should remember that the greatest demands upon girls in college are made in those years which are of far greater importance for the maturing of the female body than are any years for the growth of the male individual. In view of the frequency of chlorosis in girls who are subjected to physical or mental overexertion, and in view of the significance which the normal maturing of the female organism has for the coming generations, the physician must at least require the great majority of girls to postpone that rigid training of the mind, which usually reaches its acme in boys at about the fifteenth year, until a considerably later period. If many young women suffer shipwreck in their education and in their mental exertions, the blame is not always to be placed upon "over-

crowding," "competition," and "the opposition of obsolete ideas"; in innumerable cases it is due rather to the limits which the female body imposes upon the progressive individual. If the physician recognizes the danger in the individual case, and if his advice is of influence, he should suggest the course just indicated; he will then frequently succeed in preventing an attack of chlorosis.

Growing girls should also be protected from the early development of a sentimental imagination. If this is neglected, much harm is accomplished. As physicians it is our duty to insist, in opposition to the wishes of youth and of many an injudicious mother, that the girls should be treated as children as long as possible, and not as "young ladies." In Germany we could well follow the good old English custom, which is not so rigidly adhered to at the present time, of not only excluding growing girls under eighteen from fashionable society, exciting pleasures, dances, and the theater, but to keep them in the school room until this time. Why premature excitement of the imagination, the unnatural development of the sentimental characteristics, and early love affairs are injurious to the healthy development of the body is by no means clear. The facts exist, however, and we can not afford to overlook them.

THE CORSET. CONSTIPATION.

Although we do not agree with those who trace chlorosis to the wearing of corsets, nor with those who believe that the disease results from constipation, we believe that both these factors are deserving of earnest consideration, since they directly and indirectly prejudice general nutrition and favor the development of chlorosis.

It would be useless to demand the abolishment of the corset on account of its possible injurious effects, since it is foolish to require the execution of something which we know will not be carried out. Our efforts should be directed toward that which may be attained. Our suggestions should be of a two-fold character.

1. Young girls should postpone the use of corsets as long as possible, not employing them until the osseous skeleton is completely developed. This will prevent the great majority of the bad effects produced by this article of apparel, and particularly the malformation of the lower aperture of the thorax (see p. 410).

2. The corset should be sensibly constructed, so that it shall accommodate the natural circumference of the waist, the front and back of the corset being connected by elastic side-pieces.

The tendency to constipation, observed in older children and young girls even when chlorosis is not present, would be greatly diminished

if inappropriate corsets were forbidden. It would also be lessened if the ingested food contained a sufficient quantity of vegetables during childhood and the entire adolescent period. We have already pointed out other grounds for the necessity of such a diet. Constipation is frequently an inherited affection, and, should it make its appearance in spite of the measures indicated, it should receive careful systematic dietetic treatment. The cautious use of purgatives can not be avoided in some cases. We will return to this point when we discuss the treatment of fully developed chlorosis.

THE PROPHYLACTIC ADMINISTRATION OF IRON.

There seems to be a growing practice of giving preparations of iron to girls at the age of puberty, even though they may be in perfect health. This is true particularly in those families the elder daughters of which have been chlorotic. Newspaper advertisements which herald this or that preparation expressly advocate such a procedure. Many individuals are misled by such advice. The prophylactic administration of iron is absolutely useless; it accomplishes more harm than good. It does not prevent the development of chlorosis, as we can testify from recent experience in such cases. The great objection to the procedure is that the individuals soon become accustomed to the administration of iron. When the chlorosis does make its appearance, these patients have consequently been robbed of the best remedy. The iron fails to help them, just as is the case in patients with heart disease who have become accustomed to digitalis and who can expect no further benefit from the use of this drug.

THE TREATMENT OF THE DISEASE.

The treatment of chlorosis will be discussed under the following headings:

1. The methods which stimulate hematopoiesis. Those measures will be considered which exclusively or largely meet this indication.

2. Hygienic and dietetic accessory measures which improve the general condition of nutrition and strength. They are adjuvants to the previously mentioned methods.

3. Special methods which are indicated by the presence of complications (symptomatic treatment).

THE METHODS WHICH STIMULATE HEMATOPOIESIS.

The Administration of Iron.—Not long since Bunge claimed that the entire teaching of the curative effect of iron in chlorosis rested

upon a very weak foundation, that such a curative effect probably does not exist at all, and that all the results of the administration of iron were due to the influence of "suggestion." According to Bunge, the physicians themselves have mistaken the curative action of suggestion for the curative action of iron. These statements were stoutly contradicted at the Congress of Internal Medicine at which Bunge read his paper. In the name of generations of physicians we also must protest against this dogmatic criticism. The main evidence upon which our decision is based is not the physiologic investigations and the relatively scanty records of the increase of hemoglobin and corpuscles upon the administration of iron [243] (Gräber, Hayem, Jaquet, Laache, v. Limbeck, Oppenheimer, Reinert, Scherpf, R. Stockman). We need no quantitative examination of the blood to prove the results obtained; every physician and every layman who has eyes to see and who does not voluntarily look in other directions knows from personal and constantly repeated experience the curative action of iron and considers it as an assured acquisition to medical art. The physician, it is true, knows that iron is not a universal remedy for chlorosis; he knows that it sometimes fails completely, and that in other cases the desired effect is obtained only when the administration of iron is accompanied by other measures which remove the obstacles in the path of recovery. We are indebted to the weighty recommendations of F. v. Niemeyer for the general introduction of iron therapy into Germany, since he repeatedly pointed out that the majority of the cases of chlorosis could be cured by the administration of iron without the additional aid of dietetic and hygienic measures. With the exception of certain individuals, every clinician and practical physician of the present day recognizes the importance of iron in the treatment of chlorosis. Differences of opinion exist only as to whether iron possesses a specific curative influence—*i. e.*, whether it can be replaced by other drugs or therapeutic measures, and as to whether we should confine ourselves to the iron treatment, as recommended by v. Niemeyer, or combine it with other methods.

Recognizing the curative influence of iron, but not regarding the iron therapy as an infallible and indispensable specific at all times, we will now devote our attention more closely to the manner of its influence, to the indications for the remedy, and to the methods of its administration.

How Does Iron Act in Chlorosis?—The original answer to this question, made upon the discovery of the atom of iron in the hemoglobin molecule, was as follows: There is a lack of iron in the bodies

of chlorotics, and they are consequently unable to produce hemoglobin; if the iron is supplied by medicinal administration, the body ravenously seizes upon the metal and employs it in the formation of hemoglobin. In apparently unanswerable contradiction to this view is the fact that most girls become chlorotic although they eat well and ingest large quantities of iron (the co-called ferruginous nucleo-albumins) with their food. In a small number of instances this may not be the case, as we have already pointed out (see p. 480), but these are the exceptions. Even during chlorosis the quantity of food ingested is usually sufficient to maintain or increase the body-weight; under such conditions there can be no lack of iron. These patients, nevertheless, become chlorotic and remain chlorotic. These facts have long been recognized, and it is no longer doubted that girls developing chlorosis, and chlorotics themselves, usually receive just as much iron in their food as a healthy individual requires to maintain an equilibrium of iron. Accessory hypotheses have consequently been offered in support of the old theory. One of these (Kletzinsky[244]) supposes that medicinal iron has a stimulating effect upon the gastro-intestinal wall, which increases its digestive and absorptive power; the hypothesis is untenable, since chlorotics absorb their food in a normal manner without this "stimulant" (see p. 422). Another accessory hypothesis (Bunge[161]) is based upon the supposition of an increased putrefaction of the albumins, and has since been given up as fallacious, even by its author (see p. 419). To-day the theory of the diminished ingestion and absorption of iron, and also the theory of the reparation of the deficit by medicinal iron, have been completely abandoned. The important and interesting discovery by Kunkel[207] that, under certain circumstances, metallic iron may aid in the regeneration of the blood, only apparently favors these theories; Kunkel's experiments simply show that, where there is an actual deficiency and a demand for iron as a result of a diet containing too little of this metal and of a marked withdrawal of blood, metallic iron is a valuable accessory. These experiments, however, have not the slighest relation to chlorosis, since in this disease a lack of iron in the diet is not even to be considered. The many secondary anemias, and even pernicious anemia, could be as correctly traced to a deficient amount of iron. To prove how little a deficiency of iron has to do with chlorosis, we could also recall the fact that may chlorotics make uninterrupted recoveries without increasing the amount of ingested iron by the medicinal administration of the metal, and that the recovery may be materially accelerated by other methods than the iron therapy.

We consequently arrive at the conclusion that chlorotics receive

enough ferruginous nucleo-albumins in their diet, and also absorb them, but that they are not utilized for the replacement of the hemoglobin consumed. Why are they not employed? We must remember that blood-formation is diminished in chlorotics, and must, moreover, recognize that only a deficient function, a diminution of the energy of growth of the hematopoietic organs, is responsible for allowing the blood, with liberal amounts of the ferruginous nucleo-albumins, to pass through the system unutilized. We see the same thing in rachitis, where the cartilages and the atrophic muscles are not able to assimilate the calcium salts and the albuminous substances which are always present. As soon as we trace chlorosis to a functional weakness of the hematopoietic organs, we exclude the theory that a lack of iron causes the hemoglobin impoverishment of chlorotic blood, and that the administration of iron alone is necessary for the replacement of the hemoglobin. Strangely enough the contradiction of the two theories has remained unrecognized by many authors and others, who clearly appreciated the contradiction (Immerman, for example), but who have nevertheless failed to discover any sufficient explanation for the efficiency of the iron.

We believe that we were justified by the facts and by the theoretic requirements when we formulated the following hypotheses:[245]

1. In chlorosis the pathologic diminution of the reproductive ability of the hematopoietic organs must be overcome by a certain stimulation. There are many stimuli which are capable of producing the desired result. In the first place we will confine our attention to iron.

2. The salts of iron circulating in the blood (medicinal iron) exert a powerful stimulus upon the hematopoietic cells of the bone-marrow, and the result of this stimulation is an improvement of the quality of the blood.

3. On the contrary, the ferruginous nucleo-albumins and the proteids, which gain access to the blood, exert a much weaker stimulus; this stimulus is so slight that the ferruginous nucleo-albumins, which are present in the diet in relatively small quantities, are not sufficient to overcome the sluggishness of the hematopoietic organs.

4. In addition to the administration of iron, there are numerous other procedures which also have a stimulating effect upon the hematopoietic organs, and which consequently prove themselves curative in chlorosis.

As a supplement to these statements, it should be mentioned that the ferruginous nucleo-albumins evidently exert some stimulating effect upon the hematopoietic organs, since their administration in large quan-

tities has even been followed by recovery. We occasionally hear of good results from the drinking of blood, which at one time was quite fashionable among the young Parisian women. Hemoglobin, hemogallol, hemol, and hematogen have also been recommended. In all these substances the iron is combined in the same manner as it is in the ferruginous proteids; carniferrin assumes more of an intermediate position; while ferratin, which has recently received much attention, closely approaches to the salts of iron, since the gastric hydrochloric acid combines with it to form an iron salt as soon as it enters the stomach. The majority of these remedies require an ingenious advertisement before they are very generally employed. If we were to believe these encomiums, it would seem as though we had actually been unable to cure any cases of chlorosis before the discovery of these substances. In the face of the enthusiastic recommendation of the ferruginous proteids and of the adverse criticism of the salts of iron, v. Niemeyer's eulogium of Blaud's pills seems like an ancient chimera.

If we explain the curative action of iron only by its stimulating effect upon the hematopoietic organs, we have no difficulty in understanding why some cases can be cured in practice without the administration of iron. In all other curative methods which may be considered in chlorosis, the stimulating effect upon hematopoiesis must always be accepted as the supposed cause of recovery, since these methods have nothing to do with the chemic construction of the molecule of hemoglobin. A similar explanation will not be accepted for iron, because the chemic relations of iron to the hemoglobin always stare us in the face and, according to our opinion, obscure the true condition of affairs. According to our views, iron is but one of many medicinal and hygienic remedies which are capable of stimulating the hematopoietic organs, and not the slightest weight is to be placed upon its chemic relations to the hemoglobin molecule. In addition to iron, we will consequently consider the employment of certain other procedures which are closely related to this metal in their influence upon the hematopoietic organs.

The Preparations of Iron.—Metallic iron and the ferrous and ferric salts were the only forms in which iron was formerly employed. The ferrous salts were preferred, since they seemed to be less irritating to the gastric mucous membrane. Upon their entrance into the stomach, all of these preparations of iron are converted into ferric salts by the action of the acids; it is likely that a certain portion is immediately utilized in the formation of albuminates of iron. The combinations of the albuminates and peptonates of iron behave in almost the same manner. They are either immediately or gradually attacked by the hydro-

chloric acid; ferric chlorid arises, as do also new albuminates; a portion of the original combination may also remain unchanged. Ferratin behaves in a similar manner to the many inorganic and organic salts of iron, since it is finally acted upon by the hydrochloric acid, although it resists this action for a longer period of time.

Nothing definite is known as to the form in which the iron passes through the intestinal wall. We know only that the iron is present in the mucous membrane, in a combination which is immediately decomposed by ammonium sulphid (see p. 453); whether the iron is combined with acids, with carbohydrates, or, as Cloetta [209] supposes, with an albuminous body, is a question which must be still further investigated. After the iron is absorbed and deposited in the tissues, ferratin is formed—at least to a certain extent (Cloetta [209]).

The following groups of preparations are employed in the administration of iron: 1. Metallic iron, or iron by hydrogen. 2. Inorganic and organic ferrous salts, or their solutions and tinctures. 3. Inorganic and organic ferric salts, or their solutions and tinctures. 4. Simple combinations of the albuminates and peptonates of iron. While they are still in the stomach the acid readily combines with the majority of these preparations and true salts of iron are formed. 5. Organic compounds of iron, in which the hydrochloric acid of the stomach is either totally unable to seize upon the atom of iron or can do so only after prolonged action. This class includes the ordinary ferruginous nucleoalbumins. The preparations deserving particular mention are carniferrin, with 30 per cent., and ferratin, with 6 to 7 per cent., each, of metallic iron. The remaining substances contain a much less quantity of the metal; we will give the quantities which represent 0.1 gm. (gr. iss) of metallic iron (partly quoted from Quincke [246]):

Carniferrin	0.33 gm.
Ferratin (average)	1.54 "
Spinoferrin solution (Strohschein)	15.40 "
Spinoferrin saccharat.	20.00 "
Hemoferrum (Stearns)	20.00 "
Hemoglobin	23.30 "
Iron vitellinate (Groppler)	25.00 "
Hemogallol (Kobert)	35.90 "
Hemol (Kobert)	38.00 "
Hemoglobin extract (Pfeuffer)	71.00 "
Hematogen (Hommel)	142.00 "
Blood	166.00 "
Sanguinal (Krewel)	250.00 "
Hemalbumin (Dahmen)	277.00 "
Chlorophyll (H. Weiss)	

It is claimed that particularly the highly constituted combinations of iron are readily absorbed; this seems to be actually true of ferratin,

carniferrin, and hemogallol. Proof of the ready absorption of the remainder has not as yet been furnished.

It is specially pointed out that the iron contained in these substances is not only in a readily absorbable form, but that it is particularly adapted to assimilation. We can not see any advantage in these characteristics, since we have previously emphasized the fact that the diet of chlorotics is not wanting in assimilable iron. We must even raise the question as to whether those preparations which do not give up their iron, either in the intestinal canal or in the circulation, are not lacking in their stimulating effects upon the hematopoietic organs, and consequently in their curative effects. Four years ago we[247] expressed such an opinion, and Quincke[248] recently seems inclined to view the subject from the same standpoint. Our decision must naturally be based upon practical results. Since only large doses of the other preparations of iron have beneficial and certain effects, we should be inclined to prefer those substances in the preceding table which contain the largest quantity of iron in the smallest volume. We may consider 0.1 gm. (gr. iss) of metallic iron as the minimum dose per day; the calculations of the preceding table are based upon this amount.

6. Natural chalybeate springs.

(*a*) Chalybeate springs which contain bicarbonate of iron together with an excess of carbonic acid. In the following table are recorded the amounts of iron found in the most important chalybeate springs ("Stahlquellen") of Europe. The quantities designated are those found in one liter; the table is taken from Kisch's collection in the "Realencyklopädie" (III. Aufl., Bd. 6, S. 339, 1895):

Autogast (Trinkquelle)	0.039 gm.
Bartfeld (Hauptquelle)	0.087 "
Bocklet	0.087 "
Brückenau	0.012 "
Cudowa (Eugenquelle)	0.065 "
Driburg (Hauptquelle)	0.074 "
Elster (Morizquelle)	0.086 "
Franzensbad (Stahlquelle)	0.078 "
Griesbach (Antoniusquelle)	0.078 "
Homburg (Stahlquelle)	0.098 "
Imnau (Casparquelle)	0.052 "
Liebenstein (Neue Quelle)	0.081 "
Marienbad (Ambrosiusquelle)	0.166 "
Petersthal (Petersquelle)	0.046 "
Pyrmont (Hauptquelle)	0.077 "
Reinerz (Laue Quelle)	0.052 "
Rippoldsau (Wenzelsquelle)	0.094 "
Schwalbach (Stahlbrunnen)	0.084 "
Spaa (Pouhon)	0.047 "
St. Moriz (Neue Quelle and Paracelsusquelle)	0.028–0.029 "
Steben (Tempelquelle)	0.070 "
Teinach (Wiesenquelle)	0.081 "

(*b*) Chalybeate springs which contain sulphate of iron. The following table records the amount of sulphate of iron contained in one liter:

Alexisbad	0.056 gm.	
Levico (Starkwasser)	3.869 "	(contains much arsenic).
Mitterbad	0.440 "	
Muskau	0.090 "	
Ratzes	0.298 "	
Roncegno	3.037 "	(contains much arsenic).
Ronneby (Neue Quelle)	2.496 "	
Srebrenica (Guberquelle)	0.373 "	(contains arsenic).

The greatest weight must be laid upon the general experience of pnysicians, and, according to this standard, metallic iron, the simple organic and inorganic salts of the metal, and the chalybeate waters containing carbonate of iron, are undoubtedly to be designated as those which have produced the surest and most numerous cures. Next to these in efficiency are the waters containing sulphate of iron, and only the third place is to be assigned to the complicated ferruginous combinations, the discovery and recommendation of which rest largely upon the erroneous supposition that the salts of iron are not absorbed and are unable to do good. Our experience is not yet extensive enough to enable us to say which of these preparations will acquire the same popularity as that enjoyed by the old and well-tried salts of iron. According to our personal opinion we may give a good prognosis for ferratin, and particularly for carniferrin. Disregarding the favorable reports and our own clinical observations, our opinion is influenced by the fact that, when well borne, they can readily supply the body with large quantities of iron.

Practical Rules for the Administration of Iron.—If good results are to be obtained by the administration of iron, there are several points to be carefully observed.

1. The most important of these is not to prescribe the iron in too small a dose. This requisite of successful treatment, first pointed out and repeatedly emphasized by Immermann,[1] is now recognized by the majority of physicians. We agree with Quincke[248] in regarding 0.1 gm. (gr. iss) of metallic iron as the average daily dose. (Special reference to chalybeate waters will be found on p. 495.)

According to Quincke,[249] 0.1 gm. of metallic iron is contained in the following quantities of the iron preparations of the German Pharmacopeia:

Ferr. hydrog. red.	0.10 gr.
Ferr. sulfurat.	0.16 "
Ferr. carb. oxydulat.	0.20 "
Ferr. sesquichlorat.	0.30 "
Ferr. sulfur. oxydat.	0.36 "

Ferr. sulf. oxydulat.	0.50 gr.
Ferr. lact. oxydulat.	0.50 "
Ferr. carbon. sacchar.	1.00 "
Tinct. ferr. acet. æth.	2.60 "
Tinct. ferr. chlor.	2.80 "
Ferr. peptonat. (Dieterich.)	4.00 "
Tinct. ferr. pomat.	7.00 "
Tinct. ferr. chlor. æth.	10.00 "
Syrup. ferr. jodat.	11.00 "
Liqu. ferr. album. (Pharm.)	25.00 "
Essence of iron peptonate (Pizzala.)	25.00 "
Tinct. ferr. comp. (Athenstädt.)	50.00 "
Pil. ferr. alœt. (0.03 gr. Fe.)	3–4 pills.
Pil. ferr. carbon. (0.02 gr. Fe.)	5 pills (Blaud's pills).

This table is to be compared with the table of the ferruginous organic combinations upon page 489.

It is advisable to begin with small doses (about 0.05 gm. = $\frac{5}{6}$ of a gr. of metallic iron daily), and then to increase the daily amount rapidly to 0.1–0.15 gm. ($1\frac{2}{3}$–$2\frac{1}{2}$ gr.); in chronic cases it may sometimes be further increased to 0.2 gm. ($3\frac{1}{3}$ gr.). It still seems to us that pills are the most appropriate form of administration, although there is no objection to liqu. ferri. album.[1] or to Pizzala's popular essence of iron peptonate. Every physician has his favorite prescription, and this fact itself shows how little depends upon the particular preparation employed. The authors have long preferred Blaud's pills, or the following prescription containing iron by hydrogen:

℞.—Ferri reducti . . . . . 5 gm. (gr. lxxv).
Ext. glycyrrhizæ . . . . . q. s.
M. et ft. in pil. No. C.
Sig.—One to four pills daily.

The pills should be taken after meals, to avoid irritation of the stomach. The same precaution is to be observed with the other salts of iron, and also with the artificial solid and liquid ferruginous preparations. If strict attention is paid to this point, the pills of iron will always be well borne. There may be some temporary difficulty, but this will soon disappear. If the pills are stopped, or replaced by others of an indifferent character, the disturbances do not immediately pass away; they depend more upon the chlorosis than they do upon the iron. We do not believe that any actual difference of toleration has been proved to exist for this or that preparation; in making this statement it is assumed that the simple preparations are employed, and not those which irritate on account of their other ingredients (ethereal tinctures).

2. The second important rule is that the administration of iron should be slowly, never suddenly, discontinued. After the maximum

[1] Prepared according to the German Pharmacopeia.

quantity has been given for some time the dose should be gradually diminished, so that the iron is not entirely dispensed with until a period of about two weeks has elapsed. During this period of the diminution of the dose, either the original prepararation may be administered or it may be replaced by the tinctures containing a smaller quantity of iron. We prefer the former method.

3. There must be no interruptions or irregularities in the administration of iron. Chlorotics frequently take iron voluntarily, but they do so irregularly and do not adhere to a uniform dose. In other cases the patients frequently forget to take the iron; when they feel the effects of their neglect they increase the amount far beyond the prescribed dose, in order to equalize matters. In such instances failures are not surprising, since recovery follows only absolute regularity. A treatment that is frequently interrupted does more harm than good; it dulls the organism to the stimulating action of the iron, so that even a subsequent properly observed iron therapy is unsuccessful. It is frequently asked whether the pills of iron are to be omitted during the menstrual period; this question is to be unhesitatingly answered in the negative. We have never discontinued the administration of iron at this time, and have never seen any disadvantageous results.

4. The duration of the administration of iron should be limited. We should ordinarily calculate upon a period of six weeks—one week for the gradual increase of the dose, three weeks for the administration of the maximum quantity, and two weeks for the gradual discontinuance of the medication. In the milder forms of the disease complete recovery will be attained in this time. Improvement is noted within a few days, not in the quality of the blood, but in the disappearance of the subjective disturbances. In more obstinate cases we gain nothing by prolonging the time of administration; it is advisable to interrupt the treatment for three or four weeks and then to begin again. In the meantime, exacerbations frequently make their appearance, but the second period of administration is much more likely to cure the chlorosis.

5. In many cases of pure chlorosis the administration of iron is followed by a negative or highly unsatisfactory result. These cases are not always those which seem to be the severest; they are frequently rather mild types of the disease. If no improvement is noted after an appropriate iron therapy has been conscientiously carried out for several weeks, and if a second period of administration of iron preparations or chalybeate waters is also unsuccessful, it is unreasonable to attempt to force a cure by continuing the iron or by increasing the dose. Other methods of treatment must be adopted. Sometimes these may also be

unsuccessful, for there are cases in which the weakness of the hematopoietic organs is so great that the condition will not respond to any remedy whatever. These cases are nearly always due to a congenital hypoplasia of the hematopoietic organs, probably associated with other hypoplasias.

6. As a rule, chlorotic recurrences are more resistant to iron than are the primary attacks. In the treatment of recurrences we are more frequently forced to give up the administration of iron and resort to other therapeutic measures.

7. Iron is contra-indicated in an individual case if its administration is followed by a negative result. Repetitions of the periods of administration simply serve to prolong the course of the disease. Before we conclude that a case is absolutely refractory to iron, however, we must know that the iron has been conscientiously administered according to the principles which have just been indicated. No weight is to be placed upon the simple statement of the patient that iron has not helped her, although she has taken it in large quantities for a long period of time. In the majority of instances this means that the patient has indeed taken large doses of iron, but she has done so irregularly and the body fails to respond to the further administration of the metal. In such a case the iron is to be discontinued for about four weeks and systematic treatment is then to be instituted. Before we assume that iron is ineffectual a course of the chalybeate waters should be recommended, since it frequently happens that these waters are beneficial where the pills of iron have failed. If these measures have been exhausted, the further administration of iron is certainly contra-indicated.

We must also consider iron contra-indicated in those cases in which it is badly borne by the stomach and intestine, causing belching, nausea, vomiting, gastric pain, and diarrhea. If these symptoms present themselves we might speak of an idiosyncrasy for iron, and such cases have been frequently reported. The author, personally, has never encountered them; where such complaints existed the iron had always been given in unreasonably large doses or the proper time (after meals) had not been chosen for its administration.

If an idiosyncrasy for iron is actually present, or if other contra-indications exist to its administration by the mouth—Gastric Ulcer (see p. 463); marked vomiting, so that absorption is questionable; pronounced diarrhea—the metal may be injected subcutaneously. Such a course should be postponed as long as possible, since toxic effects have been ascribed to the subcutaneous administration of the remedy. We have

had no experience with this form of iron therapy, and consequently refer the reader to the publications of Quincke, who obtained good results from the injection of a 5 per cent. solution of the citrate (0.05–0.1 gm. = $\frac{5}{6}$–$\frac{2}{3}$ gr.) of the salt daily.

8. The chalybeate waters assume a special position in the treatment of chlorosis. Every year many thousand chlorotics go to the chalybeate springs, and an enormous percentage are cured or considerably improved. This seems striking when we consider how little iron is contained in the majority of these ferruginous waters. For example, at Schwalbach, one of the oldest and justly celebrated health resorts, a chlorotic individual drinks at most $\frac{1}{2}$ L. (1.056 pt.), or in very exceptional cases $\frac{3}{4}$ L. (1.584 pt.) of the "Stahlbrunnen." She consequently takes 0.02 to 0.03 gm. ($\frac{1}{3}$–$\frac{1}{2}$ gr.) of metallic iron into her system daily; if she always remains at the "Weinbrunnen," as is frequently the case, she receives but 0.015 to 0.025 gm. ($\frac{1}{4}$–$\frac{5}{12}$ gr.). If these quantities of iron are administered in pills or powders, nothing is accomplished. There are but two possible explanations: either the real curative agents are to be sought in accessory circumstances, or the iron is contained in the prescribed water in such a form that it is decidedly advantageous for the absorption of the metal. The second explanation is probably the more correct, since we have been convinced of the curative influence of iron and daily observe the inadequacy of the best hygienic conditions if this substance is not employed. The value of the carbonated chalybeate waters seems to be particularly due to the dilute solution of the metal, which enables the medicament to be administered upon an empty stomach. We know from experience how much this favors the absorption of other substances. For example, if the stomach is empty and 1 dg. (gr. iss) of potassium iodid is given, iodin appears in the saliva in from six to eight minutes; if the stomach is full, the iodin reaction is delayed for a much longer period of time. It may be assumed that similar conditions obtain for the absorption of the salts of iron.[1] It is certainly no whim of the attending physicians at chalybeate springs when they insist that the waters should be taken upon an empty stomach, if possible—*i. e.*, at a time when the gastro-intestinal tract exercises the most marked absorptive ability. The carbonic acid contained in the water also favors the absorption of the metal, since carbonic acid exercises a marked stimulating effect upon the mucous membrane. The early ingestion of the chalybeate water is omitted only

[1] The authors would also refer to the interesting and important observations of Köppe upon the absorption of dilute saline solutions (Naturforscherversammlung in Frankfurt a. M., 1896.

in exceptional cases (when the patients are very weak), and even then a time is selected when the stomach is as empty as possible (about three hours after breakfast or five hours after dinner). There is surely a good reason for the existence of these old and tried rules; if the experimenters who have become famous in laboratories would pay more attention to such facts gained by experience they would be stimulated to many an investigation of practical importance.

Skeptical individuals have called attention to the fact that the carbonated waters containing small quantities of iron are effective only when drunk at the health resort. This statement is undoubtedly true, and is well known to every physician. Nevertheless, it would be hasty to conclude from this that the favorable accessory conditions existing at the chalybeate spring are responsible for the greater part of the benefit derived by the patient. It is much more likely that the carbonated chalybeate water undergoes considerable change when it is placed in receptacles and kept for some time. The carbonic acid gradually escapes, simple carbonate of iron is formed and is precipitated, sinking to the bottom of the vessel; if still more carbonic acid gas is lost, hydrated oxid of iron results, which is likewise insoluble in the supernatant fluid. In addition to the escape of the carbonic acid, the contact of the chalybeate water with the organic matter of the cork aids in the decomposition of the carbonate and in the precipitation of the iron. We have frequently allowed receptacles purporting to be freshly filled with carbonated chalybeate water to remain quiet and corked for one day, after which we have uncorked them and carefully withdrawn some of the water by means of a pipet; in many instances ferrocyanid of potassium or sulphid of ammonium has failed to demonstrate the slightest reaction for iron. If the patients do not shake up the iron precipitated in the bottom of the containing vessel, they receive nothing but water free from iron. If they distribute the brown precipitate of iron by shaking the water, they receive just as much iron as is contained in the fresh water from the spring, but the iron is in quite another form and solution; it rather resembles the medical preparations of iron, but it has no effect, since it is in too small a quantity for this form of administration. In practice the water is rarely shaken, because it gives it an unappetizing appearance, and the effective substance, regarded as "dirt" by the patient, is carefully left in the bottle. The sulphuretted waters are more adapted to domestic use than are the carbonated, since the iron is not precipitated.

Although we are decidedly of the opinion that the greatest stress is to be laid upon the drinking of the fresh water at the spring, it must

not be forgotten that the sojourn at the health resort has many other advantages, the effect upon the appetite being particularly marked. This characteristic is possessed both by the chalybeate and the weak saline springs, and it is frequently manifested in a most striking manner. A stimulation of the appetite is not necessary in every case of chlorosis, a point which will be considered more in detail upon a subsequent occasion; in other patients, however, the increase of the appetite is to be greatly desired. This increased appetite could be still further utilized if less stress were laid upon the incompatability of the chalybeate water with certain articles of diet, such as fats, fruits, and acids. This teaching in reference to the fats is decidedly wrong, as we have been repeatedly able to demonstrate. To the advantage of many chlorotics, the forbidding of fats is no longer so strongly insisted upon at these health resorts as was formerly the case. The fat is limited or excluded only at the first meal after drinking the water. Later in the day it is permitted in all the larger quantity. So far as fresh fruits and acids are concerned, we should rather withhold our opinion as to whether their exclusion at these health resorts is really justified; it is likely that more individual latitude should be allowed than is customary at present. In the course of the ordinary administration of iron in powders and pills we have been frequently convinced that no injurious results follow the ingestion of fruits and acidulous foods. As previously stated, we do not care to jump to the same conclusion in reference to the chalybeate springs.

A further beneficial influence of the chalybeate springs is to be found in bathing. The quantity of iron in the bathing water is of no consequence whatever, but the amount of carbonic acid gas is of considerable importance. The refreshing and beneficial influence of carbonic acid baths (it matters not whether they contain bicarbonate of iron or sodium chlorid) can be denied by no one who has himself tried them or who has observed their effect upon weakly patients, particularly upon chlorotics. For the combating of the "irritable weakness" of the nervous system, which plays such an important rôle in the symptomatology of chlorosis, there is scarcely a better remedy. Finally, it is also to be considered that many chlorotics find much more favorable external conditions at the bathing resort, or they utilize them more, than they do at home. The correct distribution of physical rest and exercise, the fresh air, the absence of the depressing monotony of the household life, and stimulating amusements, all aid in improving the general condition.

It is impossible to estimate the values of the individual factors which

constitute the treatment at the chalybeate springs. From a therapeutic standpoint the treatment is to be regarded as a unit. We may think what we will of the significance of this or that portion of the treatment, but it is certain that many chlorotics who obtain no benefit from the iron therapy at home, in spite of favorable accessory conditions, may still expect to be cured at the chalybeate springs.

The sojourn at the chalybeate springs is usually of too short duration. If only three weeks can be allowed the treatment should not be undertaken. The result is almost always incomplete and recurrences soon make their appearance. Four weeks are sufficient for mild cases; in more obstinate ones five or six week are necessary. To extend the treatment beyond this time is to be recommended only in exceptional cases. If no result is obtained in this time, it will likewise fail to make its appearance if the treatment is longer continued.

The Administration of Arsenic.—We include arsenic among those remedies which stimulate hematopoiesis in chlorosis. Such an opinion has been repeatedly expressed in reference to other diseases; for example, so-called pernicious anemia. In healthy individuals arsenic is said to exercise a destructive influence upon the blood-corpuscles (Cutler and Bradford,[245] Stierlin,[250] Delpeuch[251]); Fenoglio,[252] on the contrary, found that in health the hemoglobin percentage remained the same or increased. Opinions are divided as to the value of the administration of arsenic in chlorosis. Wilks,[253] Isnard,[254] de Renzi[255] and Dujardin-Beaumetz[256] favor its use; Hunt,[257] Willcocks,[258] and Smart[259] found no good results, and in some cases observed exacerbations of the disease. R. Stockmann[206] expresses himself decidedly against the employment of the remedy; in 4 cases, which he reported in detail, the number of blood-corpuscles and the hemoglobin percentage showed no change while arsenic was being administered; iron immediately caused considerable improvement.

From a personal experience extending over many years we must designate arsenic as an excellent remedy in chlorosis. During the last ten years we have treated many dozen of chlorotics exclusively with arsenic, giving the patient no iron whatever, and we have been very well contented with the therapeutic results. Many of the chlorotic girls and women who were treated with arsenic remained under the same external conditions; the administration of the arsenic was not supported by improvement of the general nutrition or by other influences. The general impression gained is that energetic treatment with arsenic is usually followed by just as good results as is iron therapy, and that in no small number of cases arsenic treatment is even better

than iron treatment. We possess accurate records of the influence upon the corpuscles and hemoglobin in but 7 cases.

Observations 1 to 4 refer to patients with primary attacks of chlorosis. Cases 1 and 2 had received no treatment whatever; in cases 3 and 4 iron had been given for a long time without any visible improvement. Patients 5 to 7 had chlorotic recurrences; in the previous attacks iron had been successfully employed.

1.	Before treatment:	Blood-corpuscles	4,100,000,	dry residue	14.8 per cent.
	After 4 weeks:	"	4,400,000,	"	19.7 "
2.	Before treatment:	"	3,800,000,	"	12.9 "
	After 25 days:	"	4,550,000,	"	20.1 "
3.	Before treatment:	Hemoglobin (Fleischl)	46 per cent.		
	After 32 days:	"	75 "		
4.	Before treatment:	" (Gowers)	46 "		
	After 47 days:	"	72 "		
5.	Before treatment:	" (Fleischl)	68 "		
	After 15 days:	"	73 "		
	" 34 "	"	82 "		
	" 46 "	"	87 "		
6.	Before treatment:	Blood-corpuscles	3,750,000,	dry residue	16.6 per cent.
	After 5 weeks:	"	4,320,000,	"	19.2 "
7.	Before treatment:	"	2,520,000,	hemoglobin (Gowers)	40 per cent.
	After 28 days:	"	3,475,000,	"	48 "
	" 34 "	"	3,818,000,	"	45 "

From this time on the patient was given carniferrin instead of arsenic. Within one week the blood-corpuscles had increased to 4,400,000 and the hemoglobin to 60 per cent. In this case the ferruginous preparation was evidently more powerful than the arsenic.

Since the exclusive administration of arsenic is frequently unsuccessful, we almost always give iron in combination with arsenious acid, usually according to the following formula:

℞.—Ferri reducti . . . . 5.0 gm. (gr. lxxv.);
Acidi arseniosi . . . . 0.2 gm. (gr. $3\frac{1}{3}$);
Ext. glycyrrhizæ . . . . q. s.
M. et. Ft. in pil. No. C.
Sig.—One to four pills daily (slowly increasing).

If the case is to be treated with arsenic alone, the same prescription may be employed, omitting the iron. The initial dose of arsenic is consequently 2 mg. (gr. $\frac{1}{30}$) daily; within ten days this is increased to 8 mg. (gr. $\frac{1}{8}$). In some cases double and even three times this amount may be administered. The arsenic treatment of chlorosis, or rather the combination of arsenic with iron, has recently gained many friends; the growing use of the chalybeate waters containing arsenic (Roncegno, Levico, etc.), is evidence of an unmistakable character. From personal experience we would earnestly advise the addition of arsenic, or even its exclusive use, in those cases where iron has failed or where

it is too slow in its action. It is of still greater importance than in the administration of iron that the treatment should be continuous and uninterrupted; the dose of the arsenic should be slowly increased and then still more gradually diminished. The treatment should be continued for four or five weeks; then, as in the iron treatment, there must be an interruption of at least three weeks. The arsenic pills are to be taken during or immediately after eating.

Instead of pills of arsenic, corresponding doses of the mineral waters containing arsenic may be employed. One mg. (gr. $\frac{1}{60}$) of arsenic, the initial dose, is contained in:

8 c.c. of Roncegno water,
106 c.c. of the water of Plombieres,
115 c.c. " stronger water of Levico,
165 c.c. " Guberquelle,
1050 c.c. " weaker water of Levico.

High Altitudes.—In recent years numerous investigations have been made in reference to the influence of high altitudes upon the density of the blood, and particularly upon the number of red blood-corpuscles and upon the hemoglobin percentage. Most authors found a rapid and considerable increase of the corpuscles and of the hemoglobin when persons from the plains ascended to marked heights; upon the return to the lower level the original density of the blood again manifested itself (Viault, Egger, Köppe, F. Wolff, Mercier, Miescher[260]). Others[261]—for example, Engli-Sinclair, Zuntz, and Schumburg—found no increase in the corpuscles in the heights of the Alps. It nevertheless should be noted that the observations of Zuntz and Schumburg were made upon themselves, at a time when they were subjected to marked physical fatigue. Some authors are decidedly in favor of regarding the increased number of red blood-cells as a hypertrophy of the blood, which is to be considered as a compensatory phenomenon equalizing the diminished partial pressure of oxygen found in high altitudes. This statement has met with numerous contradictions. E. Grawitz[262] traces the phenomenon to a loss of water, which is caused by the dryness of the high mountain air. As yet no explanation seems to be sufficient; every new work brings another interpretation. In our opinion, so far as therapeutics is concerned, this question can not be decided from experiments with healthy individuals or with animals, as has previously been attempted by E. Grawitz,[262] O. Schauman and E. Rosenquist,[263] and J. Weiss[262a]. Although it may be shown that in healthy individuals only the smallest part of the marked increase of the blood-corpuscles is due to true hypertrophy, the state of affairs in patients

with a pathologic diminution of the hemoglobin percentage may be entirely different. Normal blood is so rich in hemoglobin that it can combine with sufficient oxygen in spite of the diminution of the partial pressure of the gas, but an anemic individual is seriously affected by this diminution. There is a considerable increase both in the demands made upon the heart and lungs and also in those made upon blood-formation. Until our knowledge is further extended, we are justified in supposing that permanent stimulus of the diminished partial pressure of the oxygen in high altitudes acts upon the hematopoietic organs of chlorotics and causes increased blood-production. If we adopt this supposition, we have to do with a curative power which is thoroughly analogous to iron and to arsenic. All three of these measures finally stir up the hematopoietic organs from their pathologic lethargy.

Evidence of the positive curative results of high altitudes in chlorosis is rather scanty, since there is still a lack of carefully selected material. The excellent results of the treatment at St. Moritz and other chalybeate baths of high elevation can not be quoted, since the recoveries are probably due more to the chalybeate water than to the high altitude. Nevertheless, we know some chlorotics who had previously visited other chalybeate baths without actual benefit and who were then cured at St. Moritz, where the influence of the elevation was combined with that of the waters. It would be worth the trouble to investigate further the importance of high altitudes in chlorosis, and the results would be as interesting theoretically as they are practically important. Naturally, we do not expect a recovery, and particularly a permanent one, in every instance. This is also the case in the iron treatment. Sometimes we are successful in permanently overcoming the sluggishness of the hematopoietic organs; in other cases the pathologic atony soon returns after the removal of the stimulus (iron or high altitude, as the case may be).

The Withdrawal of Blood.—Upon first thought it would seem preposterous that anyone had thought of treating chlorosis by the withdrawal of blood. We have heard the most scathing criticisms from authoritative sources of "this new and degenerated edition of the vampirism of bygone days." We by no means favor the practice of venesection in chlorosis, but will only point out that this bold measure is neither so paradoxical nor so ridiculous as it seems. The history and the practical results of venesection in chlorosis are fully related in the publications of A. Dyes. Since 1883 Dyes [263] published several dissertations, in which he most warmly recommended venesec-

tion in severe chlorosis. He supported his claims by a rich practical experience that we must recognize, and by theories which are so lacking in scientific foundation that we must refrain from their discussion. In the meantime, Wilhelmi,[264] Scholz,[265] Schubert,[266] and, to a certain extent, Krönig,[267] have announced themselves as champions of the new theory. The entire clinical material favorable to the new treatment has been recently collected in the monograph of Schubert[266] Like Scholz and others, this author emphasizes the fact that the venesection should be followed by a systematic course of sweating. Scholz says that the course of sweating is frequently curative without a preceding venesection. Nonne and P. Schmidt[268] have no unfavorable results to record, but they have also had no such good results from venesection and from sweating that they would care to recommend the new therapy in place of the old and tried treatment with iron. We have personal knowledge of about 6 cases in which venesection undoubtedly had a beneficial influence; 2 cases in particular occur to us in which venesection caused a rapid and complete recovery, after the chlorosis had been previously treated unsuccessfully for months with iron. These experiences are not sufficient for the foundation of an accurate personal opinion.

The general opinion, which is based upon the previous publications, is that there is no reason for giving venesection a prominent position in the treatment of chlorosis. In this respect we entirely agree with Nonne and P. Schmidt. There is still less reason, since the treatment with venesection and sweating is by no means simple, and, according to the opinion of its own champions, must extend over a long time and frequently requires to be repeated. Upon the other hand, it would be entirely wrong simply to deny and ridicule the favorable results which have been obtained. We have to do with facts, and facts are always to be respected.

The only theory which, to our mind, seems adapted to explain the curative action of venesection is the one which we have adhered to for a long time and which has been given in this article: that there is deficient blood-formation in chlorosis, and that all our measures must be directed to arousing the hematopoietic organs from their pathologic lethargy. With this theory we explain the curative action of iron, of arsenic, of high altitudes, and now we return to it again to explain that of venesection. It seems to us that one of the best supports of this theory is that it enables us to understand such a heterogenous collection of curative methods. We do not know how anyone who traces chlorosis to a lack of iron, and who would make the cure of the disease de-

pendent upon the replacement of this deficit, could explain the other treatments, and particularly the results of venesection, without utilizing the most daring accessory hypotheses.

According to our theory the curative action of venesection is readily understood. Of all physiologic conditions, we know of no more important and effective means of stimulating blood-formation and of causing a stormy reaction of the hematopoietic organs than acute hemorrhage. We might assume that the same influence is exercised in chlorosis. If healthy individuals are bled, the loss of hemoglobin is simply replaced; in chlorosis it is possible that, if the proper time is selected, the hemoglobin percentage may rise until it reaches the normal. The lethargy of the hematopoietic organs is overcome by the energetic procedure and does not return; in favorable cases hematopoiesis continues until the normal condition of the blood has been attained. Further experience is necessary before it can be determined at what time in the course of chlorosis we may expect good from venesection, the particular indications for the procedure, and how much blood is to be withdrawn (heretofore the amount has been about 100 c.c. = $3\frac{1}{3}$ oz.). Even at the present time, however, we can not deny, either from a practical or theoretic standpoint, that venesection is a dangerous, but in skillful hands also a useful weapon (v. Noorden).[269]

The Treatment with Extracts of Organs.—It is with great hesitation that we refer to the recent efforts to cure chlorosis by feeding the patients with organic extracts. The subject is much too new for us to hold an opinion in reference to its value and to its future.

The Treatment with Red Bone-marrow.—We have had some personal experience with this treatment, but our results did not encourage us to continue the experiments. Fresh red marrow may be given, or tablets of the same may be employed. In the English literature we find a publication by Ch. Fobbes,[270] who reports good results.

The Treatment with Splenic Extract.—A Berlin firm has recently placed a preparation upon the market, which is manufactured from the spleens of cattle. This substance has been given the name of "eurythrol." M. David[271] has treated a number of chlorotics with this preparation, and states that the experiments were, on the whole, successful and encouraging.

The Treatment with Ovarian Extract.—In view of our adopted theory that the condition of the "internal ovarian secretion" has a relation to the pathogenesis of chlorosis, we must consider the treatment with "ovarin" to be full of promise. Experience alone can decide this question. The publications are still very scanty. Spillman and Etienne[272]

treated 6 chlorotics with ovarian extract, and assure us that they saw most favorable results. Fredeli[273] employed the "ovarin" (prepared by E. Merck, of Darmstadt) in doses of 0.25 to 0.5 gm. (gr. iv–viij) *pro die*, and was likewise pleased with the result. The brief papers by Muret[273a] and Touvenaint[273b] are also encouraging.

We have considered the administration of the extracts of the organs at this place because their curative influence—if its existence is subsequently confirmed—can only be due to the indirect stimulation of the hematopoietic organs.

DIETETIC AND HYGIENIC TREATMENT.

The remaining accessory methods employed in the treatment of chlorosis assist only indirectly in the recovery, since they are simply directed toward the improvement of the nutritive condition and of the general strength. These measures alone are not sufficient, for chlorosis frequently makes its appearance when nothing has been neglected in this direction, and we often observe that the disease persists in spite of the most appropriate diet and the best care until iron has been administered. Upon the other hand, we can not fail to recognize how little can be accomplished by the iron treatment, or by some of the previously mentioned substitutes, if they are opposed by unfavorable nutritive conditions or by faulty methods of life. We must consequently consider how these factors can be best arranged for chlorotic patients.

THE DIET.

It has been previously stated in this article that in chlorosis the metabolism of the albumins, as well as metabolism in general, is not characterized by any actual deviations from the normal. The nutritive condition is consequently dependent upon the same laws as it is in health; the ways and means by which it may be influenced are indeed subject to variation.

The problem which presents itself is not always the same. There are numerous chlorotics whose nutritive conditions are entirely normal, both in regard to the subcutaneous fat and to the musculature. In these individuals we would not undertake to change the quantity of the food ingested, although improvements might seem possible and desirable in reference to the quality and the distribution of the diet. In a second group of patients we find that the nutritive conditions are bad; such conditions may have existed from youth or they may have first made their appearance during the development of the disease. In these cases one of the foremost problems of the treatment of the chlorosis is to improve the condition of nutrition. To do this it is, of course, neces-

sary to study carefully the peculiarities of the individual case and to gain an exact knowledge of the factors responsible for the bad nutritive condition. In the anamnesis we should obtain what might be called the dietetic history of the patient as far back as possible. In a third, and by no means insignificant, group we have to do with girls and women whose forms are more rounded than normal and who give us the impression of obesity, or, at least, they are what the layman designates as "puffy." These cases offer a rich field for dietetic treatment, but it is to be undertaken only after a careful consideration of the individual nutritive conditions and habits of life.

We will first consider those dietetic principles which are applicable to all chlorotics, and then take up those variations which are demanded by the peculiarites of the individual case.

Regularity and Frequency of the Meals.—We regard regularity in eating as one of the most important rules. As we have already seen, very many chlorotics sin in this respect, since they only play at eating at the regular meal-time; between meals, however, they eat according to the whim of the moment and are at times almost ravenous. This bad habit must be decidedly opposed, or control is lost of the amount of food actually ingested, and we cultivate the dangerous hysteric tendency of the chlorotics, which makes them the weak playthings of their own sensations. Chlorotics should eat and drink only at the time prescribed by the physician; within a few days the irregular ravenous appetite will then disappear.

The intervals between the meals should not be very great, never amounting to more than two and a half or, at most, three hours; the longest interval should follow the dinner. The following is a correct arrangement:

Breakfast at 8 A. M.	Dinner at 1 P. M.
Early luncheon at 10.30 A. M.	Late luncheon at 4.30 P. M.

Supper at 7.30 to 8 P. M.

The greater frequency allows of a diminution of the amount ingested at the individual meal. This is an important point, because very many chlorotics suffer from a hypersensitiveness of the stomach and their appetites are soon satisfied. Under certain circumstances the number of the meals may be still further increased; this is necessary when it is important that the patient should eat as much as possible, or when the stomach is able to digest only very small quantities of food at one time (see p. 515).

The Amount of Albumin in the Diet.—Whether the chlorotic be lean, well nourished, or corpulent, the total of food ingested should

contain a large percentage of albumin. At this place we wish to oppose the view frequently expressed at the present time, that the people require only a relatively small quantity of albumin, and that when this is supplied it matters not whether they are given carbohydrates and fats or more albumin. It does not matter, so far as the formation of fat is concerned, since this process is dependent exclusively upon the number of calories contained in the diet. If, however, we wish to strengthen the entire body, build up new tissues containing albumin, and stimulate blood-formation, experience teaches that we must prescribe a diet rich in albumin. In this respect we can learn more from the careful observation of patients upon different diets than we can from experiments upon metabolism. One hundred gm. (3⅓ oz.) of albumin is the minimum daily amount of albumin required by chlorotics; if the individual is corpulent, a somewhat larger quantity, about 120 to 140 gm. (4–4⅔ oz.), is necessary. If the desired quantity can not be reached with the ordinary foods, some of the albuminous preparations may be employed (somatose, nutrose, protogen, eucasin).

Meat in the Morning.—We must not only consider the amount of the albumin, but also the time of its ingestion. In all anemias, and particularly in chlorosis, we can not speak too strongly in favor of the introduction of substances rich in albumin into the diet of the early morning hours. The present custom in Germany, of eating a scanty breakfast containing little albumin, is not suitable for many patients, and is particularly detrimental to chlorotics. Almost all the patients feel most depressed in the morning hours; they lounge about and are capable of no actual exertion. This condition, which is disagreeable to the patient and prejudicial to her proper training, can not be better counteracted than by adopting the English custom of commencing the day with a meal that is as strengthening as possible. If this rule is conscientiously observed, most girls overcome the sensation of wretchedness and the tendency to fainting so frequently observed in the morning hours.

In addition to the results of practical experience there are also interesting theoretic reasons why the first meal should be rich in albumin. The products of the digestion of the albuminous bodies are rapidly taken up into the circulation, and may be utilized by the organism within a short period of time. This is not true of the carbohydrates and of the fats. The fats are very slowly absorbed, and several hours pass before even a part of these substances can pass into the circulation. Carbohydrates are rapidly absorbed, but they can not be immediately employed by the tissues, since only a very small portion

gains access to the arteries of the body, the larger quantity being first arrested in the liver. From the liver they are allowed to escape into the blood only very gradually, so that the amount of sugar in the arterial blood after a meal rich in carbohydrates is no greater than in the fasting condition. It is the albuminous bodies alone that are consumed soon after their ingestion. This peculiarity is of special value for our present purpose. Alcohol is the only other substance which is consumed so soon after its ingestion (see p. 508).

In view of these facts we would recommend that chlorotic girls and women eat a large portion of meat at their breakfast; it does not matter whether the meat be cold or warm, or whether a roast, smoked meat, wild fowl, or fish is selected. In practice, in Germany at least, most can be accomplished with cold meat (cold roast, cold birds, smoked meat, and particularly raw or boiled ham). The amount to be eaten is to be prescribed by the physician and not left to the whim of the patient. We begin with 50 gm. (1⅔ oz.) of beef (weighed in the prepared state), and gradually increase the amount to 100 gm. (3⅓ oz.), if possible. Since meat soon satisfies the appetite of the patient, the other articles of diet must take up as small a volume as possible; for example, two pieces of toast or of zwieback that is free from sugar (the "All Heil" or "Nährtoust" prepared by Otto Rademann, of Bockenheim-Frankfurt a.M.). The ordinary zwieback, containing sugar, is not to be recommended. To this may be added a small cup of tea or of coffee with a little milk or sugar.

We have treated but few chlorotic girls who did not immediately say that it was quite impossible for them to eat meat. The physician must expect to meet with this opposition, and a certain amount of firmness will soon overcome this idea. After a short period the objection will be silenced, and the good result will show that the demand was justified.

The Employment of Milk in Chlorosis.—The laity, together with many physicians, are inclined to give milk a very prominent position in the diet of the chlorosis. Milk is, without doubt, a very useful and, under certain circumstances, even an extremely important and indispensable article of diet. Nevertheless, when milk is prescribed certain points are always to be considered, and the daily amount of the milk and its distribution must be accurately stated. Much harm can be accomplished by the simple command to "drink plenty of milk." In chlorosis the harmful influence may be manifested in three ways: 1. If large quantities of milk are ingested at inappropriate intervals, when there is a marked loss of appetite, the remainder of the diet suffers,

often to the extent that the total amount of food ingested (including the milk) is not sufficient to replace the body waste. Emaciation results instead of the desired increase in weight. 2. In chlorotics with an average appetite the milk diet easily leads to overfeeding. In anemic persons, however, this influence is not limited to the laying on of fat, but the amount of water in the tissues of the body is increased and the patient acquires a bloated appearance. The anemia is not improved by the increasing corpulency; practical experience rather shows that recovery is delayed. 3. If milk is taken frequently between meals, as is so frequently the case, the stomach is maintained in a full condition throughout the entire day. This favors the tendency of the stomach to relaxation and dilation. According to our experience, we are convinced that gastric dilation in chlorosis is partly due to the ingestion of unreasonably large quantities of milk.

There is scarcely ever any objection to be raised to the ingestion of smaller quantities of milk (about $\frac{1}{2}$–$\frac{3}{4}$ L. = 1.056–1.584 pt.). Milk should be chosen as an actual nutritive factor only when hyperesthesia of the stomach gives rise to disturbances upon the ingestion of solid food or when lean patients are to be fattened. In both cases it is better to replace the milk by a mixture of milk and sweet cream (Stüve[247]). If equal parts of milk and good cream are taken, 1 L. of the mixture has a nutritive value of about 1300 calories—*i. e.*, the nutritive value corresponds to that of 2 L. of good milk. The amount of fluid, however, is only half as great, and the appetite and the muscular strength of the stomach are spared. The high percentage of fat is never injurious, as we can state from an extended experience; we have employed the mixture of milk and cream not only in the secondary gastric disturbances of chlorosis, but also when the case has been complicated by the presence of gastric ulcer.

Alcohol in Chlorosis.—It is more than doubtful whether alcohol has a stimulating effect upon hematopoiesis. Such an opinion, however, is very widespread; this power is particularly attributed to red wine, since the public, in a most superficial and ridiculous manner, believes that its red color holds some relation to the red color of the blood. Nevertheless, alcohol is largely in evidence in the diet of chlorotics, particularly in well-to-do families. Alcohol has a comforting influence; it is quickly absorbed and counteracts momentary sensations of weakness. It consequently happens that many chlorotics frequently take a small quantity of strong wine at intervals throughout the day, particularly in the morning, when they feel most miserable. The small amounts are increased, and sometimes a considerable quantity is in-

gested. The same result could have been attained in a perfectly harmless manner by a sensible arrangement of the meals and by the eating of a liberal amount of albumin at breakfast (see p. 506). In chlorosis alcohol can usually be dispensed with as an actual stimulant. However, alcohol can be very advantageously employed as an aid to the formation of fat in lean chlorotics; it favors the laying on of adipose tissue to such an extent that it is immaterial whether the individual eats 7 gm. (128 gr.) of fat, or drinks 9.3 gm. (149 gr.) of alcohol. Moreover, alcohol is better adapted to stimulate the appetite and to increase the ability to digest fats than is any other medicine. Upon the whole, alcohol is consequently to be more frequently recommended in lean than in corpulent chlorotics. The amount is always to be accurately designated.

Fresh Vegetables in Chlorosis.—We have already pointed out that a lack of fresh vegetables can aid in the development of chlorosis (see p. 480). The quantity of vegetables seems to us to be even more curtailed in the diet of chlorotics than it is in the diet of healthy children and of growing young girls. We have seen a large number of chlorotics, particularly from the western part of Germany, from France, and from North America, whose physicians have strongly forbidden them to eat green vegetables (probably with the exception of spinach and of carrots), stewed fruit, and particularly fresh fruit. The reason for such a prohibition is that the nutritive values of vegetables and fruits are supposed to be so insignificant that the appetite should rather be directed to more nutritious foods; it may also be due to the idea that vegetables and fruits are harmful to the sensitive stomachs of chlorotics and interfere with the administration of iron. We must decidedly contradict any such objections.

The nutritive value of the green vegetables is indeed small when expressed in calories; they may be made exceedingly nutritious, however, by proper preparation with cream and butter. The nutritive value, moreover, is not to be considered only from the caloric standpoint. In addition to the material which is capable of oxidation, vegetables and fruits also contain many other substances which are useful and indispensable to the body—the so-called nutritive salts or other equally important combinations of iron (see p. 480). We have never observed that vegetables and fruits decrease the capacity for the ingestion of other nutritive substances; on the contrary, the great variety which is offered makes it possible to increase the total supply of food.

Too much stress is laid upon the detrimental effect of vegetables upon the stomach. Without doubt vegetables are to be excluded if the

chlorosis is complicated by the presence of a gastric ulcer. In all other gastric disturbances, whether they are in the form of hyperesthesia, cardialgia, anorexia, or flatulence, whether marked symptoms of gastric atony are present, or whether the stomach secretes too much or too little hydrochloric acid, neither green vegetables nor stewed or even fresh fruit are contra-indicated. The pathologic disturbances are, at least, not increased, and they are frequently improved as soon as the previously excluded vegetables are added to the diet; the latter would be capable of little variation if they were to be permanently withheld.

The improvement in the gastric symptoms and the disappearance of the constipation, which may have been present, are often surprisingly rapid and can not be sufficiently praised by the patients. It is true that chlorosis is not cured in this manner, but much has been gained if troublesome sequelæ have been prevented. The advice to prescribe the more frequent use of vegetables and of fruits in chlorosis should be taken earnestly to heart, or it will frequently happen that a medical or clerical champion of vegetarianism will take the case from the family physician and obtain a better result.

An appropriate arrangement of the vegetables is as follows: A generous quantity of green vegetables is given at the midday meal; according to the requirements of the individual case, these may be prepared with much or little butter; according to the condition of the stomach, they may be cut up into small pieces or served in the ordinary form. A considerable quantity of fruit may be eaten at 4.30 P. M. as a second luncheon. That fruit is to be employed which is in season; fruits with small seeds, however, should be avoided if the stomach is sensitive. In winter the dried fruits are to be recommended; they may now be bought almost anywhere, and if they are of the best quality and skilfully prepared they are scarcely to be differentiated from stewed fresh fruits. Fruit preserved with sugar is much less worthy of recommendation. Whether fresh or stewed fruit is selected will depend upon the circumstances of the individual case; stewed fruit is better borne by the stomach, since it is rapidly converted into a homogeneous mass, while fresh fruit is taken into the stomach in large pieces and causes a more marked mechanical irritation.

Bill of Fare.—If we have to do with an average case, in which there is no special indication for the accumulation of fat or for sparing the stomach, the dietary may be arranged somewhat as follows:

Breakfast.—An abundance of meat. For the composition of the breakfast, see p. 507.

After breakfast the chlorotic should rest a short time, about a half-

hour or an hour, either in bed or upon a sofa; we very much dislike to dispense with this rule, and only do so when external conditions make its observance impossible. During this time many chlorotics fall asleep, and this should be encouraged by darkening the room and by avoiding disturbing noises.

For the *first luncheon*, which must be small in quantity, we are governed by the needs of the individual case, choosing one or two eggs (prepared as desired), some toast or zwieback with butter, and ¼ L. (½ pt.) of milk or of milk and cream (see p. 507). If the case requires it a dessertspoonful of cognac or of "Kirschwasser" (best given in the milk), or a very small glass of sherry or of Madeira may be allowed.

Dinner.—Whatever the patient may do between breakfast and dinner, we must always take care that she either sits or lies quietly at home for at least twenty or thirty minutes before eating. If she comes home just before dinner, tired out by her work, irritated by the cares of the city, or heated from a walk, the ingestion of food favors the appearance of gastric disturbances.

At dinner the chief weight should be laid upon the eating of an abundant amount of meat and fresh vegetables. The chlorotic should be allowed to choose from the remaining food upon the table, according to her appetite. If there is little desire to eat, it may be necessary to forbid soup or to have it follow the meat course. There is usually considerable thirst, since according to our régime but little fluid is taken during the morning. The patient should satisfy this thirst only toward the end of the meal, since otherwise the nutritive supply will suffer. Water may be drunk, or, when prescribed by the physician, water with wine.

This meal is likewise to be followed by rest in the recumbent position for from three-quarters to one-and-a-half hours. If gastric disturbances are present this time may be utilized for the purpose of applying warm applications to the abdomen (dry heat or cataplasms).

The *second luncheon* consists either of plenty of stewed or fresh fruit with wheat bread, zwieback, or simple tea-biscuit, or, if fruit is to be avoided, the patient may have a small cup of tea or cocoa with wheat bread, toast, zwieback, simple tea-biscuit and butter. If there is no tendency to the excessive formation of acids by the stomach, honey and jelly may also be permitted. This small meal may be followed by ¼ L. (½ pt.) of milk or of a mixture of milk and cream.

The supper should be as simple and unirritating as possible. At least four times a week the main dish should be a thick soup or broth

made from oats, barley, grits, rice, tapioca, or buckwheat; this should sometimes be prepared with bouillon and butter and sometimes with milk and butter. These may be occasionally replaced by other farinaceous foods or puddings; stewed fruit may be given several times weekly. If these articles are not sufficient to satisfy the appetite, the patient may eat bread and butter, fresh cheese, cold meat, or some other trifle. On the other days the main dish may be eggs or articles containing them, or even meat or fish. If the amount of food ingested in the evening is unsatisfactory, it may be complemented by from 0.3 to 0.5 L. (½–1 pt.) of milk, or of kefir, which is to be taken immediately before retiring. If the milk is omitted, a half-bottle of well-fermented beer is to be recommended after supper.

The chlorotic should retire at 10.30 P. M., at the latest. The prolongation of the day into the late hours of the night is injurious for all forms of anemia.

These suggestions as to the daily program and as to the quality of the food will usually be sufficient. Whether the amounts of the individual foods and drinks are to be specified will depend upon the effect of the diet upon the nutritive condition of the patient; all that is usually necessary is to prescribe the quantities of the articles eaten at breakfast and to limit the amount of milk, as we have indicated in the preceding scheme. Unless we are forced to do so, it is not advisable to pursue this subject further and to weigh practically every mouthful ingested by the patient. This only makes the patient appreciate her illness all the more acutely, and such a possibility is always to be avoided. If, however, the weight of the patient shows that she eats too much or too little when left to herself, the exact measurement of the amount of food to be ingested should not be long neglected.

It is not always possible to carry out these measures accurately, because many chlorotics are not in such a position that they can live altogether for the benefit of their health throughout the entire course of the treatment. The course which has been outlined is to be regarded as the ideal dietetic treatment which is to be adopted to support the administration of the iron. If ideal conditions can not be attained, the principal important points must be borne in mind. These points are: 1. The manner of the distribution of the diet. 2. A large supply of albumins in general. 3. A generous supply of albumins in the morning hours in particular.

Without considering the actual complications of chlorosis, it may be necessary to vary the diet on account of unusual emaciation, a tendency to obesity, or pronounced gastric disturbance. In all of these cases it

is usually necessary to give very exact quantitative directions in reference to food and drink. We will not attempt to give a list of diets, because successful results are attained only by the strictest attention to the details of the individual case. Some general observations are, however, necessary.

The Diet for Unusual Emaciation.—Anorexia or gastric disturbances are almost always present; if this were not the case, emaciation would scarcely have made its appearance. It frequently suffices to place the patient under the influence of new surroundings and of a diet rich in variety; they then eat more of their own accord and soon gain in weight. This peculiarity is very frequently observed in patients who are in a bad state of nutrition when they enter the hospital; the ordinary hospital diet requires but few additions to cause an increase of several pounds in the body weight within two or three weeks (see p. 442). Many other cases are not improved by such simple measures; they require a systematic course of feeding. These cases require those foods which do not overload the stomach; they must contain a high nutritive value in a small volume. This is best attained by increasing the easily digested fats (cream, butter, oil of sesame, cod-liver oil). The supply of albumin need not necessarily be increased above the ordinary daily amount of 100 to 110 gm. ($3\frac{1}{3}$–$3\frac{2}{3}$ oz.). The carbohydrates and vegetables should be prepared with as much fat as possible. We do not consider it advisable to give the carbohydrates a prominent place in the dietary; they are simply to be utilized as accessories. The number of the meals must frequently be increased; this is best accomplished by giving milk early in the morning, before rising (about an hour before breakfast), and late in the evening, before retiring. The use of alcohol is important.

The Diet to be Employed When There is a Tendency to Obesity and Retention of Water in the Tissues.—During the existence of the chlorosis it is not advisable to attempt actually to reduce the fat; obesity treatment always require the greatest caution when employed in youthful individuals. It is much better to wait until the chlorosis has been cured before an attempt is made to reduce the obesity. In the meantime care should be taken that the diet does not cause a further accumulation of fat. This is to be accomplished only by a most careful study of the previous diet. It will usually be found that the diet was altogether too rich (frequently as the result of unreasonably large quantities of milk). Only the excess should be cut down; if the diet is so arranged that it furnishes about 30 to 34 calories to the kg. (2.2 lb.) of body-weight, the excessive loss of fat in young girls

will be just as surely avoided as will any considerable accumulation of adipose tissue.

In those chlorotics who have a tendency toward obesity, however, there is also another very important point to be considered. In almost all anemic persons, and particularly in chlorotics, the increased amount of fat is associated with an abnormal accumulation of water in the tissues (see pp. 402, 455). In spite of perfect functional activity of the kidneys, the patients have a puffy appearance and tend to have edemas. The tissues are rich in water not because of renal insufficiency, but because the water is retained in the blood, and particularly in the tissues. It is true that chemic examinations of the tissues have not been made, but the results attained by limiting the amount of water furnish evidence of an unmistakable character. These patients are usually girls who have been drinking large quantities of milk and who have excreted a correspondingly large amount of watery urine (see p. 508).

In such cases we regard it as one of the most important therapeutic problems to remove the water from the tissues. The excessive amount of water in the tissues is an obstacle to recovery and opposes the favorable influence of the iron therapy. After the removal of this water we have frequently seen a chlorosis disappear when it had previously resisted energetic treatment with iron. We are very much inclined to place the good results obtained by sweating (see p. 502) upon a parallel with those which follow a diet in which the amount of water is limited.

The weight will show how much water may be accumulated in the tissues without any indication of actual edema. If the amount of water taken by these corpulent and puffy-looking chlorotics is limited to about 1200 c.c. = 1.267 qt. (not including the water in the solid foods), the body-weight rapidly falls; the amount of urine remains large or is even increased, as is the case in the "dry treatment" described by Oertel for edematous heart cases. The loss in weight is due entirely to the extraction of water from the tissues, since the amount of oxidizable food corresponds to the demand, thus precluding combustion of any of the fat. The losses of weight which we have observed varied between 4 and 8 kg. (8.8 and 17.6 lb.) within two or three weeks. Although these cases received no iron, almost all the disturbances disappeared during this time; this was quite marked in reference to the dyspnea, palpitation, and sense of fatigue.

The Diet for Gastric Disturbances.—If gastric disturbances are present the dietetic measures must be changed accordingly. We

agree with v. Niemeyer, Immermann, and others, that gastric disturbances do not contra-indicate the administration of iron, but we do not go so far in such cases as to neglect the gastric disturbances and to expect to cure these individuals with iron alone. We have become convinced from an extensive experience that the nutritive disturbances which result from the neglect of the gastric symptoms work against the cure of the chlorosis; and, *vice versâ*, the recovery is greatly aided by adapting the diet so that all of the digestive powers may be utilized.

The subjective symptoms are much more marked in chlorotics than would be expected from the objective examination of the stomach and of the gastric digestion. Some pathologic processes are at work in the stomach, as is shown by the frequent hyperacidity, the rarer subacidity, and the atony which may amount to dilation.

As a result of the gastric disturbances there is a diminution of the amount of food ingested and some emaciation makes its appearance. The therapeutic points to be observed are practically those which have been considered under the dietetic treatment of unusual emaciation, but owing to the sensitiveness of the stomach to overloading the distribution and multiplication of the meals must be carried still further. We have always found it well to feed severe cases regularly at two-hour intervals, so that from 8 A. M. until 10 P. M. eight small meals are taken. In saving the stomach, it seems to me to be of special importance to separate the solid from the liquid foods; in accordance with this principle, liquid food and more solid nutriment are given alternately. The amount of the liquid should never exceed ¼ L. (½ pt.), and the intermediate solid food should never weigh more than 100 gm. (3½ oz.). In order to obtain the highest nutritive value in the smallest volume, cream and butter are to be used as generously as possible. Many patients who had been previously placed upon the scantiest diets on account of violent gastric disturbances received in this manner a daily amount of about 150 gm. (5 oz.) of fat; they bore it very well, gained rapidly in weight, and lost their gastric disturbances in a short time. We have frequently pointed out that the easily digested fats should not be banished from the diet of patients with gastric disturbances; their exclusion from the dietary of gastric disturbances, evidently of a secondary nature (as in chlorosis), is, in our judgment, a grave error which most seriously endangers the nutrition and strength of the patient.

With the exception of iron, medicinal treatment is usually superfluous. Nevertheless, it can not be denied that hydrochloric acid (twenty minutes before eating) sometimes increases the appetite and facilitates the ingestion of food. We have seen this result of hydro-

chloric acid even in patients who suffered from hyperchlorhydria during the digestive period; hydrochloric acid after meals would be of value only if the secretion of hydrochloric acid was diminished. Extr. strychni in combination with extr. bellad.[1] is more frequently of value than is hydrochloric acid. The first of these is one of the best remedies for mild degrees of atony of the stomach, and the latter dulls the gastric hyperesthesia to a much greater, and to a much less harmful, extent than the opiates. They are both given in solution or in pills, three or four times daily, before eating. Only a small number of pills should be prescribed at one time, since only the soft and freshly prepared pills are to be employed.

If either hyperchlorhydria or atony is present the stomach may occasionally be washed out, but brilliant results are not to be expected. This measure does good only when the food is retained in the stomach for an unusually long time. The best time for lavage is about 7 P. M.; at 8 P. M. the patient should receive a small quantity of broth, and at 10 P. M. $\frac{1}{4}$ L. ($\frac{1}{2}$ pt.) of milk and cream.

The Treatment of Constipation.—If at all possible, special treatment of the constipation is to be avoided. A sensible diet and mode of life corresponding to the demands of the individual case will usually suffice to regulate the condition of the bowels. A generous quantity of vegetables and fruits has a particular influence in this direction (see p. 509). If so much harm has been done by an inappropriate diet in the past that the constipation persists in spite of a new dietary, the milder laxatives may be employed. Those substances are best which may be taken in the evening and which cause a movement of the bowels upon the following morning (tamarinds, laxative teas, Curella's Brustpulver, Hufeland's powder for children, rhubarb powder combined with an alkali). In practice enemata are usually the first remedies employed, because they are supposed to be the least harmful means for facilitating the action of the bowels. It is impossible to determine how this opinion ever originated; but it is wholly incorrect, and the opposite is true. If the habitual constipation of chlorotics is treated with enemata the malady will be made worse than ever.

The treatment of the constipation, however, must not degenerate into an actual laxative treatment of the chlorosis. There has been no lack of opinions favoring such a course. These opinions are based upon the theory that chlorosis is dependent upon intestinal decomposition (see p. 419). The same idea has caused other writers to lay the greatest emphasis upon the "disinfection of the intestine"—the

[1] According to the *German Pharmacopeia.*

labor of a Sisyphus! Creosote, naphthalin, β-naphthol, thioform, and many other substances have consequently been added to the list of antichlorotic remedies (A. Pick,[274] Ch. W. Townsend[275]). These remedies are temporarily employed in certain localities, but they have never acquired any importance outside the practices of individual therapeutists.

PHYSICAL EXERCISE.

It is impossible to give general rules as to the amount of physical exercise which should be required of chlorotics. In the past the general tendency has been to cause these patients to exert themselves as much as possible, and sufficient physical exercise, particularly in the open air, was advised as an important accessory measure to stimulate hematopoiesis and cure the chlorosis. Recently, on the contrary, much stress has been placed upon saving the strength as much as possible. Hayem,[276] Nothnagel,[277] M. Mendelsohn,[278] Albu,[279] and the more recent works upon practice have even pointed out the advantage of long-continued rest in bed.

In the decision of this question it is of the utmost importance that we should not be influenced by the temporary popular opinion. The proper solution is to be found only in the study of the individual case.

In severe and moderately severe cases it is always well to commence the treatment with absolute rest in bed. The patients often object strenuously to this, but in a short time the rest is regarded as a great benefit. Many chlorotics are annoyed by the constant struggle between their desires and their physical inability to gratify them; the rest in bed ends or diminishes this combat. The frame of mind is improved, serious disturbances soon disappear, self-confidence and confidence in the treatment returns, and the observance of the dietetic and medicinal measures is facilitated. Rest in bed is to be particularly insisted upon if serious complications are present. It is self-evident that patients with thrombosis, gastric ulcer, cardiac dilation and weakness, or frequent and long-continued attacks of amaurosis belong in bed; a tendency to edema of the feet and to frequent attacks of dizziness and unconsciousness require the same prescription. The result obtained must determine the duration of the rest in bed. We would not recommend that a chlorotic should be kept in bed any longer than is absolutely necessary. In ordinary cases, which demand absolute rest on account of the severity of the disease in general and not on account of existing complications, two or three weeks will usually suffice; in rare instances four or five weeks or even a longer period of time may be

necessary. The transition from absolute rest to active exercise should be gradual.

In the milder cases, which constitute the majority, and in convalescence from severe chlorosis, the patients should rest at least several hours every day. We do not mean by this that the patient is to prolong the night into the day and to remain in bed until late in the morning. This result is to be better attained as follows: while the patient is still in bed between 7 and 8 A. M., according to the season of the year and the custom of the house, she is to be given a glass of milk (300–400 c.c. = $9\frac{1}{2}$–$12\frac{1}{2}$ oz.). A half-hour later the patient rises, dresses herself, and takes breakfast with the family (for the composition of the breakfast, see p. 510). After breakfast the patient again lies down, either in bed or upon a comfortable sofa; experience shows that many patients fall asleep during this period, which should be of about an hour's duration. A second rest is to be prescribed for the hour following the dinner. In the evening the patient should retire two hours after supper, and never later than 10 P. M. This division of the day is to be recommended wherever the saving of the patient's strength is indicated; it should also be rigidly observed at the chalybeate baths.

Numerous cases of chlorosis recover without any such saving of the patients. Everyone knows this, but the fact should not be employed as an argument against such measures. It is important that the physician should bear those measures in mind which produce the most rapid and certain recoveries. Unfortunately, circumstances prevent us from always carrying out that which we look upon as desirable, and concessions must frequently be made, particularly in reference to the subject under discussion. We should, however, not fail to recognize that the cure of the chlorosis is delayed if the strength of the patient is not saved and if she is allowed to wander about at her own pleasure. The truth of this statement is definitely proved by the numerous chlorotic girls who are admitted to the public hospitals. A few days in bed are sufficient to ameliorate the entire condition and to cause the disappearance of the headache, dizziness, attacks of unconsciousness, nausea, and loss of appetite.

As soon as the chlorotics regain their strength, muscular exercise in the open air may be prescribed for the milder cases. This should not be carried to excess, or the entire success of the treatment will be jeopardized. From a general hygienic standpoint it is a most excellent thing that the young women of to-day are more inclined to sports and to outdoor exercises than were the members of the preceding generation. This free exercise of muscular power is to be permitted only in per-

fect health; in the case of the chlorotics, who need their strength, the amount of muscular exertion must be just as definitely prescribed by the physician as are the hours of rest.

HYDROTHERAPEUTICS.

The tendency of the times is toward the extensive employment of hydrotherapeutic measures. Although this movement does not always originate from professional sources, the physician should also make use of these measures in the treatment of chlorosis. Much to the detriment of the patient they are too infrequently employed; and the danger is imminent that, because of this, the lay public will come to place hydrotherapeutics in a certain contrast to scientific medicine, whereas it is only one of its useful adjuncts. The careful study and appreciation of hydrotherapeutics by the practical physician would surely save many patients, and no small number of chlorotics, from the extreme and harmful procedures to which the physicians and laymen who practise hydrotherapy, with some brilliant exceptions, are only too easily inclined.

Cold Baths and Douches.—In chlorosis all hydrotherapeutic measures which extract heat from the body should be avoided. This group includes tub baths at a temperature lower than 32° C. (89.6° F.), and with certain exceptions, also river- and sea-bathing. In the milder cases river-bathing (swimming) may be allowed in midsummer if the water attains a temperature of 22° C. (71.6° F.), and if the air is warm at the same time. For sea-bathing the water should have a temperature of a least 20° C. (68° F.), and the air should also be warm. Neither the river nor the sea baths should be of more than a few minutes duration. The bath is to be followed by a vigorous rubbing of the skin. Chlorotics are very sensitive to cold baths; they are frequently chilled for a long time after the bath and lose appetite and sleep. We can do no more than to add our warning[269] against cold baths to those of Muroi[25] and of O. Rosenbach.[1]

All forms of hydrotherapy which produce a marked shock are to be avoided in chlorosis. Such are the cold douches and many varieties of friction with cold water. They increase the nervous excitability of the patient.

The following treatment is to be recommended:

Cold Rubbings in a Modified Form.—The best time to be selected is just after the patient has drunk her milk and while she is still in bed. The back is to be rubbed several times with a wet rough towel (temperature about 20° C. = 68° F.), and this is to be followed by brisk friction with a rough cloth until the skin is dry, warm, and

red. More importance attaches to the subsequent friction and reaction of the skin than to the preceding moist rubbing. After the patient lies down the arm and the corresponding side of the breast are to be treated in a similar manner, and the procedure is to be continued by degrees until the entire body has been bathed. Only one portion of the body is bare at one time, and it is again covered as soon as the rubbing has been completed. After the entire body has been gone over in this manner the patient is to remain in bed for a short time.

Friction carried out in this manner is one of the best means of improving the peripheral circulation. The favorable influence upon the sensitiveness to cold, and upon the rapidly changing sensations of heat and chilliness, are unmistakable; the tendency to headache, palpitation, and pains in the limbs are also combated.

These frictions may be carried out in all cases of chlorosis, being well borne in the severe forms. They are not necessarily to be neglected at bathing resorts, where the patients take the mineral baths several times a week; they may at least be taken on those days when the full baths are omitted. During menstruation, or at least during the first two days, the frictions should not be given.

Warm full baths may be prescribed upon two days in the week, provided that they can be taken at home. The temperature should be 34° C. = 93.2° F., and the duration ten minutes. The best time for this bath is between 5 and 6 P. M. After the bath the patient should go to bed and remain there until supper time. Certain substances may be added to the bath water which have a slightly stimulating action upon the skin (sea-salt, lye, extract of pine-needles). If domestic conditions do not allow of the bath being taken at home, it is best omitted in cases of moderate severity; if the patient can not rest in bed after the bath, it is followed by mild depression and relaxation lasting several hours instead of the expected refreshing stimulation.

Mineral Baths.—By mineral baths is meant the baths in which free carbonic acid is given off in bubbles. This property is possessed by all of the carbonated chalybeate springs (Schwalbach, Rippoldsau, Pyrmont, Driborg, St. Moriz, etc.), and by numerous brine baths (Soden I. Th., Nauheim, Homburg, Kissingen, Marienquelle in Marienbad, Tarasp, and many others). Carbonated baths have also been artificially prepared, but in spite of great advances in the technic they have not attained the completeness of the natural carbonated springs.

The virtue of all of the carbonated springs used for bathing purposes depends entirely upon the contained carbonic acid, and it does not matter whether the other substance in the water is iron or sodium

chlorid. If the baths alone are to be considered, we might just as well send our chlorotics to Soden and Nauheim as to Schwalbach and Rippoldsau (Hughes,[280] E. Hirsch[281]). As has been previously pointed out, however, it is of at least as much importance that the patient should drink the fresh water of the chalybeate spring (see p. 495).

It is not necessary to dwell upon the importance of carbonated baths, since the most important facts have been previously stated. On account of their excellent effect upon the general condition they are among the most useful remedies for the treatment of chlorosis. They possess the property of stimulating the nervous system, without subsequent relaxation, to a much more marked degree than do the ordinary full baths or the non-carbonated brine baths, and, vice versâ, they are able to quiet any excessive irritability.

The employment of carbonated baths is indicated in almost every case of chlorosis in which the strength will permit of the use of baths in general. Caution must be exercised in severe cases, since the patients not infrequently are attacked in the bath by dyspnea, palpitation, and even by dizziness. This is due to the fact that the air over the water contains a large amount of carbonic acid. This has no deleterious effect upon healthy individuals, but chlorotics, who have difficulty in obtaining sufficient oxygen for their tissues on account of the diminished quantity of hemoglobin in their blood, suffer from the high percentage of carbonic acid in the inspired air. They are not only in danger of becoming unconscious—a circumstance of rare occurrence—but for several hours after the bath they remain in a condition of anxious excitement. In these bathing resorts this is largely to be avoided by covering the tubs and by securing good ventilation of the bath rooms. In many places, however, the technical appointments leave so much to be desired that patients with only mild degrees of chlorosis can not take the carbonated mineral baths without suffering from some of these annoying symptoms. These conditions are to be regretted in proportion to the strength of our conviction of the efficacy of the baths.

Nothing can be said in a general way in reference to the number of baths. Many physicians are in the habit of sending their patients to the chalybeate springs with the direction that they shall take a definite number of baths; the patients go to the baths with a time schedule, as it were, and consider themselves unfortunate or the entire treatment a failure if, for some reason or other, they can not reach the stated number of baths. We consider such directions as thoroughly reprehensible. It can never be told in advance how the patients will stand the baths; even if they have taken them before, the condition of affairs may be

quite different upon a subsequent occasion. The carbonated baths have such varied effects upon different individuals and must be so modified in frequency, temperature, and duration according to their influence upon the body, that a medical control at the bath can not be neglected. In the interests of the patient we would say that it is deplorable if the physician believes that he can direct the course of the bath treatment from the home of the patient, and consequently practically advises the patient to avoid the physician at the baths.

As a rule, the conditions are so arranged that the patient takes three or four baths a week; those who take more than five baths a week are rare exceptions. The average duration of the bath is from twelve to fifteen minutes; the temperature varies between 31° and 33° C. = 87.8° to 91.4° F. After the bath the chlorotic should lie down and rest, in contrast to many other patients, who are directed to take a half-hour's walk after their bath.

Recently iron-brine baths have been recommended in chlorosis, and the managements of the sanitariums at the chalybeate baths have done everything in their power to procure facilities for giving brine baths. Our impression is that these efforts are not particularly praiseworthy, as far as the treatment of chlorosis is concerned. In certain complications, such as diseases of the sexual organs or obstinate muscular pains with neuralgia, the brine baths may be quite valuable; in uncomplicated cases of chlorosis the chalybeate baths are entirely sufficient.

The details of the treatment at the springs and baths are to be found at p. 497.

Sweat baths and other diaphoretic treatments for chlorosis were first employed in connection with venesection. Dyes,[263] Wilhelmi,[264] Scholz,[265] and Schubert[266] regard the marked perspiration which may easily be produced by hot packs after venesection as the chief benefit to be derived from the withdrawal of blood. Scholz seems to have been the first to have made systematic use of diaphoretic procedures without venesection in chlorosis. The treatment by sweating is likewise recommended by Könne,[282] Dehio,[283] and, with certain limitations, also by Nonne[268] and P. Schmidt. Lenhartz[284] and O. Rosenbach[1] are decidedly opposed to such procedures.

We have had too little personal experience with the diaphoretic treatment of chlorosis to form an opinion of its value. From the statements of authors, it seems to have been established that the sweating at least does no harm; excellent results indeed seem to have been obtained in numerous cases by the diaphoretic treatment. The so-called sweat

beds or similar appliances may be employed; one of the good ones is known as the "Phœnix." Hot baths with subsequent hot packs are also recommended. After the sweating, Dehio directs that the body should be rubbed with warm dry cloths.

How much of the result is due to the sweat bath and how much to the accessory circumstances (rest in bed, administration of iron, venesection, etc.) can scarcely be determined. We regard the question as one that has not been decided.

We are just as much in doubt as to the explanation of the curative influence of the sweating. One of the first suppositions was that deleterious substances were excreted in the perspiration (Könne); no proof of this statement has ever been offered. We are inclined to the opinion that the dehydration of the tissues has something to do with the result. In a previous chapter it was pointed out that many chlorotics collect too much water in their tissues, and that it is desirable to remove this excess. We would consequently place the diaphoretic treatment in the same class as the treatment with a dry diet (see p. 513). Until our practical experience has become more extended, however, theories are of secondary importance.

SEXUAL LIFE.

The question has been raised as to whether chlorosis did not have an important bearing upon the regulation of the sexual life. In a general way the question may be answered absolutely in the negative.

The only important point is whether chlorotic girls should be allowed to marry. Practical experience has long since given its decision. In any mild case of chlorosis no one would think of forbidding marriage, and it is even claimed, with a certain amount of justification, that the regular sexual life aids in overcoming the chlorosis. This experience agrees with our adopted theory, that metabolic processes in the ovaries have some bearing upon the origin of chlorosis. With the introduction of the sexual life, from its beginning to pregnancy, puerperium, and lactation, the genital glands are stimulated by influences that were previously foreign to them, and which, we may suppose, exert a powerful influence upon the metabolism of these organs. According to our theory, hematopoiesis must also derive some benefit from this chain of events (see p. 355).

In severer cases of chlorosis it is better to postpone marriage until the disease has been cured. If we should expose these cases to the demands of young married life and housekeeping we should be violating our adopted principle, that chlorotics should be spared as

much as possible. It is only in exceptional cases that such a possibility is to be considered. As a matter of fact, it frequently happens that young girls marry while they are still markedly chlorotic or immediately after they have recovered from the greatest severity of the attack. Injurious consequences do not fail to make their appearance. A severe recurrence very frequently places the young wife upon a sick-bed in the first year of married life; abortion, endometritis, and hysteria are then quite likely to become manifest. In these cases sexual intercourse does more harm than good; so long as the chlorosis is present the wife is less capable of enjoying sexual relations, and frequently suffers severely from the demands made upon her. This may be the source of nervous disturbances of the most varied nature, which only too frequently cause the young wife to become hysteric.

Under certain circumstances, as stated, it may be necessary to postpone marriage on account of chlorosis; true chlorosis, however, is not an actual obstacle to marriage. It would be so were it definitely known that the chlorotic girl would be permanently sterile. In many cases chlorosis occurs in association with a hypoplasia of the genitalia that may be so extreme that impregnation and reproduction are out of the question. In these cases, however, it is the hypoplasia of the genitalia and not the chlorosis which is the cause of the sterility.

The objective examination must decide whether the genitalia of the chlorotic are in a hopelessly undeveloped state and constitute an obstacle to marriage; from the nature of things, however, it is only in the rarest cases that this examination is made before marriage.

SYMPTOMATIC TREATMENT.

Having considered the general treatment of chlorosis, we will now turn our attention to the treatment of certain individual symptoms. Some of these have already been considered; for example, the treatment of the disease when it is complicated with severe gastric disturbances, with constipation, and with certain skin diseases.

Headache.—Ordinarily the headache of chlorotics requires no special treatment; it calls for the same therapeutic measures as those which are employed against the chlorosis. Sometimes, however, the headaches are so violent and obstinate that their relief becomes a matter of primary importance.

Medicines are to be used as little as possible, and only when results can be obtained by such simple remedies as valerian and peppermint. The effectiveness of the stronger medicines, such as antipyrin, phenacetin, salipyrin, and antifebrin, is soon exhausted; their use has a ten-

dency to cause both physician and patient to increase the dose constantly, and to employ in rapid succession the oldest and the newest remedies without ever attaining the desired result. The antinervines and the antineuralgics are indicated only when the headaches occur in intermittent attacks; in these cases they bring such certain and rapid relief that it seems barbarous not to employ them to shorten the attack. They should, however, be avoided in the severer forms, where the headache is continuous, dull, and stupefying.

Where these constant headaches are present, the treatment that never fails is continuous rest in bed. Even after a few days there is considerable improvement, and after a week at most the headaches entirely disappear. It is, of course, to be understood that while the patient is in bed she is to be spared from all exciting influences. In the beginning of the treatment the curative measures should consist chiefly of generous nourishment, the patient being fed every two hours; in addition to this, iron or iron and arsenic are also to be given. Alcohol is to be avoided. As soon as the greatest severity of the attack has passed, hydrotherapeutic measures, such as cool spongings and lukewarm baths, are indicated; when first instituted these procedures are followed by slight exacerbations.

We must also mention the fact that lumbar puncture has recently been recommended for the severe headaches of chlorosis (Lenhartz[285]). The advocates of venesection state that excellent results are also obtained in such cases by the withdrawal of blood.

Neuralgia.—The neuralgias of chlorotics are to be treated in exactly the same manner as are the headaches. If the neuralgias are intermittent the employment of the old and new antineuralgics is not only permissible, but, on account of their prompt action, actually indicated. The deleterious effect of small amounts of these substances upon the body is insignificant when compared with the beneficial results obtained by quickly relieving the attack. Morphin is to be avoided.

For the much more frequent neuralgic pains that do not occur in definite attacks, rest in bed has proved itself to be the best remedy; it should be accompanied by the energetic administration of iron and particularly of arsenic. It is advisable to support this treatment with wet hot packs; hot baths with subsequent free perspiration are also to be recommended. Excellent results are also obtained from the use of mud baths and by a prolonged sojourn in a high altitude (St. Moriz).

Although electrotherapeutic measures are still held in high repute by some authorities, their use is but rarely followed by permanent results.

The intercostal neuralgia of chlorotics holds a position peculiar to itself; this has been fully discussed at p. 408. We were recently told by a chlorotic, who suffered from an evidently hysteric left-sided intercostal neuralgia, that the neuralgia had been completely cured ever since her body had been exposed to the action of the *x*-rays.

Fainting Attacks.—If unconsciousness and dizziness frequently make their appearance in the course of the chlorosis, the physician should insist upon the placing of the patient absolutely at rest in bed. When such a course is pursued, beneficial results are not long in making their appearance. If it is believed that permanent rest in bed can be dispensed with, or if external circumstances make its employment impossible, the best results will be obtained by a rigid regulation of the diet; the meat breakfast, which we have previously recommended, is of special value in these cases, and it is also advisable to feed the patient at intervals of two hours. A moderate amount of wine, taken in small doses during the course of the day, is an important adjuvant.

The individual attack may frequently be terminated by immediately placing the patient in a horizontal position and giving her several drops of some ethereal solution. At this place we wish to call attention to the superiority of acetic ether, which is considerably more effective than the ordinary sulphuric ether, not only for the fainting spells of chlorotics, but also for the much graver attacks of dizziness, oppression, and asthma of cardiac and nephritic patients. We have small gelatin capsules prepared which contain 0.20 to 0.25 gm. (gr. iij–iv) of acetic ether (Rosenapotheke, Frankfurt a. M.); these may readily be carried by the patient and taken when they are needed. As a rule, one capsule is sufficient to prevent the fainting attack.

If the tendency to fainting is not overcome, the attack of unconsciousness is to be treated according to the well-known principles: dorsal position with elevation of the limbs, loosening the clothing, particularly the corset, rubbing of the chest, and bathing the forehead with Cologne water or with other ethereal or alcoholic solutions. More vigorous measures, such as the injection of camphor or ether, are but rarely necessary.

Cutaneous eruptions dependent upon chlorosis usually disappear under the combined administration of iron and arsenic (see p. 438). Certain eruptions, however, are unusually obstinate, and this is particularly true of acne. This is most frequently observed in chlorotics between sixteen and eighteen years of age. Relief from the disfiguring affection is a matter of great importance to the patient.

In addition to iron and arsenic, which are always to be employed

in a periodic manner, energetic treatment with hot baths and subsequent sweating is to be recommended. The diet should contain a generous quantity of vegetables; if the condition of the digestive organs will permit, a pure vegetable diet may be adopted for some weeks. The simultaneous administration of sodium chlorid should not be neglected, since this is one of the most important requisites for the success of the vegetarian treatment and for the avoidance of deleterious results. The greatest attention must be directed to obtaining regular evacuations of the bowels.

Quick results are never to be expected in the treatment of chlorotic acne. If, however, the measures which have been suggested are patiently carried out, a cure will certainly be accomplished.

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LYMPHATIC LEUKEMIA

BY

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LYMPHATIC LEUKEMIA.

INTRODUCTION.

THE word leukemia is used to indicate a disease the characteristic symptom of which is an increase of white blood-corpuscles in the circulating blood, associated with hyperplastic changes in the blood-making organs.

At the beginning of the study of leukemia, two forms were differentiated, namely, lienal and lymphatic, depending on whether the spleen or the lymph glands were found enlarged, and this division was adhered to by many, even till our day. Nevertheless, observing the blood-making organs carefully by the aids that modern microscopy offers, we find very little to sustain this old division. So long as our knowledge of the various forms of leukocytes, of their source and of the origin of the blood generally was debatable, as it was before Neumann's discovery of the blood-making properties of the bone-marrow, it was unimportant whether the division of the different leukemias was based on the gross clinical symptoms or the histogenesis of the blood changes. The small-celled forms were of lymphatic origin, and were so designated on account of the accompanying enlargement of the lymph glands, while the others were of lienal origin, since they were accompanied by enlargement of the spleen. True, Virchow's differentiation of lymphatic and lienal leukemia had a histogenetic significance, for the smaller mononuclear cells found in lymphatic leukemia were attributed to the lymph glands, and the larger, usually polynuclear, cells found in the other type of the disease to the spleen. With Neumann's demonstration that the bone-marrow was the principal seat of origin of the blood, particularly of the leukocytes, the old classification became impossible, for in both forms alterations were almost constantly found in the bone-marrow, and following this, the majority of cases of leukemia became referable to it. So far the diagnosis had depended on the increase of leukocytes in the blood and the finding of a splenic tumor (lienal leukemia) or a swelling

of the lymph glands (lymphatic leukemia), while now the alterations in the bone-marrow, discovered post mortem, demonstrated a myelogenous participation. Depending on the kind of alteration in the bone-marrow, two varieties of leukemia were differentiated (Neumann), one associated with a lymphadenoid change in the bone-marrow, corresponding in great part to the present lymphatic leukemia, the other associated with a pyoid change which included almost all the cases designated as lienal.

In spite of the great advance which Neumann's discovery brought about, there was still little appreciation of the relation of the three forms of leukemia. Several things were opposed to a clear understanding of this relation, namely, our defective knowledge of the histology of the blood, and the impossibility of separating the different forms of leukocytes or of finding their seat of origin. Virchow had already attempted the elucidation of this problem, but after his division into lymphocytes and large white blood-corpuscles his efforts proved futile.

A strictly scientific separation of the different kinds of leukocytes, with the explanation of their histogenesis, was first made by Ehrlich. We are now in a position to recognize from the study of the blood during life in what manner the blood-making organs are diseased. Moreover, we find that exactly as Virchow's differentiation of leukocytes confirmed Neumann's discoveries, two kinds of leukemia are to be separated, one characterized by an increase in lymphocytes associated with an increase in the lymphadenoid tissue, the other by a definite change in the bone-marrow, and an increase in blood elements that are evidently myelogenous in origin.

Though, according to our present knowledge, true myeloid tissue seems to be normally limited to the bone-marrow, lymphatic tissue appears to be one of the most widespread histologic elements, not, it is true, in amount, but in ubiquity. In large amounts it is generally known as lymph glands, or on mucous membranes, as lymphoid tissue; yet in small amounts it is found everywhere in absolutely normal organs, in the blood-making, such as the spleen and bone-marrow, as well as in all other organs (Arnold, Ribber).

It is therefore possible that even apart from the lymph glands any lymphatic structure may prove the principal seat of the alteration, namely, the tonsils, the lymphatic apparatus of the intestine or the spleen. All these forms of lymphatic leukemia show a common bond in the *lymphemic blood-picture*, and represent a single disease more or less differentiated by certain gross peculiarities. The common, and, from a clinical standpoint, the most important symptom is the alteration of the blood. From this the disease takes its name, and accordingly, under a

strict nomenclature, we have a lymphatic leukemia (or possibly better, with Walz, a lymphocytic leukemia) with predominant participation of the lymph glands, a lymphatic leukemia with special participation of the lymphatic apparatus of the intestinal tract, of the spleen, of the bone-marrow, etc. Thus we have a sufficiently clear classification which takes into consideration the different organs participating without a strict examination of the blood changes, provided they are in a general way similar. The difference is mainly this, that our division, based on the frequent confirmation of Ehrlich's work, is histogenetic and not merely anatomic. We thereby get rid of the former obstinate controversy as to the propriety of speaking of a gastro-intestinal, cutaneous or other form of leukemia. The blood-picture shows the kind of leukemia (whether lymphatic or myelogenous); the findings, especially the clinical ones, in the organs indicate only the locations responsible for the disease.

Lymphatic leukemia, therefore, is a disease the principal symptoms of which consist in the blood alteration (characterized by an increase in lymphocytes) and the tumor-like enlargement of lymphatic structures. In this increase of lymphocytes in the circulation less depends on the absolute number of these cells than on the percentage increase in comparison with the rest of the leukocytes. In other words, it is not the simple numeric ratio of the leukocytes to the red blood-corpuscles (W : R) which constitutes the basis for a diagnosis of "leukemia," for there are simple polynuclear leukocytoses in which the relation W : R may be much more abnormal (Leonard and Lloyd Roberts, Petrone). As Ehrlich has taught, the principal factor is the qualitative deviation of the leukocytic increase from the normal—in other words, the specific pathognomicity of the leukocytosis.

Looking at a large number of cases of lymphatic leukemia, we find all possible gradations from the most marked increase in leukocytes to an almost normal number. This transition is indicated by examples of every degree, from cases with a marked lymphemia (lymphatic leukemia) to those with a slight or no absolute increase, in which the abnormal blood-picture consists only in a relative increase of lymphocytes in comparison with the other white blood-corpuscles.

This brings us to that other disease known as *pseudoleukemia*, which name expressly indicates its non-identity with genuine leukemia. This is characterized by the absence of the special morphologic symptom, namely, the increase in leukocytes. All the other symptoms, however, particularly the anatomic, agree with those of lymphatic leukemia, the only thing lacking being the increase of leukocytes in the blood.

Still, when we study the blood-picture in a large number of pseudoleukemia cases (*e. g.*, the observations of Westphal, the cases of Pfeiffer, Fröhlich, v. Notthafft), the differentiation of these two diseases, on the basis of the blood-morphology, is by no means so simple; for we find a considerable number showing evident signs of a deviation of the blood from the normal, represented always by a relative increase in lymphocytes. We must therefore consider the blood-picture as inadequate for a differentiation of lymphatic leukemia and pseudoleukemia. Moreover, the foundation of this differentiation is readily shaken when we remember that the general notion of pseudoleukemia was conceived at a time when the fine anomalies of the blood were as yet unrecognized, and leukemia itself was not narrowed down to the limits of to-day, but comprised all high-grade increases in the white blood-corpuscles, and only these. Finally, it is significant that even in earlier times the boundary between these two diseases was undetermined and the decision was frequently considered to lie at the will of the observer (Winiwarter). Since this time the idea has repeatedly been expressed that we have to do here with closely allied processes, and for proof of this we have, on the one hand, the intermediate forms which, characterized by a moderate lymphocytosis, may be called by either name; on the other, the reported transitions of pseudoleukemia into genuine lymphatic leukemia.

Nevertheless, as we will show in a later section (Diagnosis of Pseudoleukemia, p. 625), the boundaries of pseudoleukemia must be defined more accurately than they have been during the thirty years since its first description. Later observations demand a sharper definition of the disease. After the separation of all the dissimilar affections, a group of cases still remain which alone deserve the name; and on account of the similarity of the blood-picture and the general clinical symptoms to lymphatic leukemia, these may possibly be comprehended with it in the same description.

In spite of these transitions and in spite of the uncertainty into which the advances in blood histology have brought the differentiation of genuine lymphatic leukemia from the diseases with lesser lymphocythemia, we must still regard both as separate affections. We are not yet in a position to pass a decisive judgment, but there seems to be too great a difference between the outspoken cases to bring them together on account of an apparent common histogenesis. New investigations must and will open up new points of view. It is possible that the future may develop subdivisions, and so close the gaps in our knowledge of the morphology, pathogenesis and etiology.

We designate by the name *lymphatic leukemia* a disease characterized

by an increase of lymphadenoid tissue in the organs and an increased number of lymphocytes in the blood. This symptom-complex presents two varieties, differentiated as acute and chronic lymphatic leukemia.

The rapid course of acute leukemia, its fatal termination in a few weeks with evidences of profound prostration and degeneration of the organs, and the inconspicuousness of the lymphoid processes even in cases with markedly lymphocythemic characters of the blood, give this disease the features of an acute infection.

Chronic lymphatic leukemia develops in a period varying from months to years, is characterized by a gradually increasing and, finally, marked lymphomatosis, and becomes fatal through either cachexia or a terminal increase of the leukemic process simulating the acute form —that is, of course, provided the end is not brought about prematurely by complications, intercurrent disease or compression of vital organs, especially the respiratory or circulatory.

As is evident from this short summary, we have to do with two different affections with a common location and lesion, or with one affection manifesting the same anatomic symptom-complex, yet running a course sometimes acute, again chronic. With the elucidation of the etiology we are led to expect that we shall discover whether we have to do here with the same pathologic process running different courses or with different diseases showing similar pathologico-anatomic lesions.

ACUTE LYMPHATIC LEUKEMIA.

THE definition of acute lymphatic leukemia comprehends all the acute leukemia cases so far known. There is no case described without prejudice which shows other than a lymphatic blood-picture or manifests its principal change in any blood-making tissue other than the lymphatic. In all acute leukemia cases designated as myelogenous or lienomyelogenic, this name has not the significance attributed to it in our introduction. On the contrary, this designation was based on the localization of the gross anatomic changes, thereby saying that the bone-marrow alone or only the spleen and bone-marrow were affected, while a swelling of the lymph glands was wanting or was clinically slight. Since, however, the designation should be applied not on account of the gross anatomic appearance, but on account of the histologic findings, we can not admit the former as sufficient grounds for such a nomenclature. On closer investigation we find that the affected organs invariably show a new formation of lymphocytes, sometimes of the small variety (ordinary lymphocytes), again of the larger (large lymphocytes). The large lymphocytes correspond to the forms designated by many observers in these cases as marrow cells.[1]

Just as it is unjustifiable to designate these cells marrow cells (since they occur in the bone-marrow in large numbers only in these leukemic hyperplasias), so should the finding of an acute leukemia with sole participation of the bone-marrow be regarded as insufficient reason for calling it myelogenic. The name *myelogenic* or, better, *myeloid* (see section on Myeloid Leukemia) indicates from our standpoint not simply origin from the bone-marrow, but origin through hyperplasia of definite bone-marrow elements. The meaning of the word is not to be sought in its literal translation, but it is to be regarded as a technical term with a sharply defined significance, just as *lymphatic*, according to our way of speaking, does not simply indicate origin from a lymph gland, but

[1] The name "marrow cells" (Müller) was introduced on account of their occurrence in large numbers in the bone-marrow of acute leukemia. On account of their location and their similarity in form they were for a time confused with Ehrlich's myelocytes, the early stages of the polynuclear neutrophile leukocytes. They are, however, positively differentiated from these both by their form and staining properties, and by their completely different manner of development (see P. I., pp. 48, 51).

origin from a tissue which produces a definite cell-form known in general histology as lymphocytes. [The views of some of those who combat the author's opinions will be referred to later.—ED.]

In the cases described by previous observers as acute myelogenic leukemia, the hyperplasia of the bone-marrow was invariably composed of small or large lymphocytes.

Moreover, in these cases it is not to be thought that the bone-marrow alone constituted the seat of origin of the leukemia, but it is probable that the rest of the lymphatic apparatus participated also in the hyperplasia, and that a clinical or anatomic enlargement of the lymph glands, spleen or other lymphatic structures was prevented by the rapid removal of their products by the circulation. This conclusion is supported by the fact that all the cases described by Neumann as pure myelogenic leukemia with lymphadenoid hyperplasia of the bone-marrow, so far as they can be controlled by the descriptions given, are to be reckoned with acute leukemia. In the same way, cases of acute leukemia in which no gross change was found in the blood-making organs, and which have been reported in support of the theory of the origin of leukemia in the blood itself (Hirschlaff), are to be explained by the assumption that the rapid removal of the elements allowed no collection of lymphatic tissue to come into existence, not even in the bone-marrow.[1]

That a certain amount of irritation, produced possibly by the mechanic process of the removal of the newly formed lymphatic cells, may be brought to bear on the true myelocytes and be manifested by the appearance of isolated myelocytes in the blood of these cases may be granted. Nevertheless, the hyperplasia of the lymphadenoid tissue, wherever localized, constitutes unexceptionally the principal factor in acute leukemia.

[The views of those who oppose the teaching of Ehrlich and his pupils may be profitably introduced in this place. Some difference of opinion will exist so long as the final definition of the bone-marrow cells remains uncertain. There can be no question at all regarding the occurrence of cases in which the bone-marrow is the only seat of discoverable change, and it seems established by those who have specially studied the histology of the marrow that this structure is really a lymphoid tissue with the capability of making lymphocytes. Since no case of acute lymphatic leukemia has been studied in which lesions

[1] The cases of Leube and Fleischer, and of Heuck commonly quoted as evidence for the occurrence of leukemia without an anatomic basis show all the essential lesions of the bone-marrow.

were found in the lymphatic glands alone, the conclusion seems obvious that the marrow is most probably the invariable place of origin of the disease.

Dennig[1] describes a case of acute leukemia without discoverable alteration in the blood-making organs. The patient was a servant girl, aged nineteen years, whose illness began about the end of August and whose death occurred on October 2d. At first the condition was regarded as chlorosis, the hemoglobin being from 25 to 30 per cent. In two weeks it had fallen to 20 per cent., and the blood was then carefully examined, with the discovery that the leukocytes numbered 1 to 40 red corpuscles, the total number of the latter being 800,000. There was no enlargement of the glands or the spleen. An hour before death the number of white to red corpuscles was 1 to 2. The stained preparations showed marked preponderance of lymphocytes, especially the small forms. The autopsy showed no visible change in any of the blood-making organs. Dennig's case is cited here because in subsequent examinations of the specimens Walz[2] claims to have found decided changes in the marrow. He does not agree with the view of Ehrlich and his followers regarding the origin of leukemia. Basing his opinion on a case of lymphatic leukemia in which the lymph glands were unaffected, he says that he believes we are not justified in regarding lymphatic leukemia as a disease of the lymphatic glands alone. The bone-marrow belongs to the lymphatic apparatus in a certain sense and is normally able to form lymphocytes. It must therefore be concerned in lymphatic leukemia in common with the spleen, lymphatic glands, and various lymph nodes. Among others who have reported cases of acute lymphatic leukemia without change in the bone-marrow are Körmöczi[3] and Hirschlaff.[4] Of course, it is always possible that a more complete examination might reveal lesions in such cases, though Hirschfeld insists upon the thoroughness of the search in his case.

Pappenheim[5] describes 2 cases of lymphemia without enlargement of the lymphatic glands. The first was a case of acute leukemia in a woman of thirty-five years. The blood-count showed 1,024,000 red corpuscles, 20,000 leukocytes, and 28 per cent. of hemoglobin. The differential count showed 1.5 per cent. polynuclear, 2.5 per cent. large lymphocytes, 96 per cent. small lymphocytes. There was a moderate poikilocytosis and many macrocytes and normoblasts, but no megaloblasts. The postmortem

[1] *Münch. med. Woch.*, 1901, No. 4.
[2] *Centralbl. f. Path. u. Allg. Path. u. Path. u. Anat.*, 1901, No. 23.
[3] *Deutsch. med. Woch.*, 1899, p. 238. [4] *Münch. med. Woch.*, 1898, p. 942.
[5] *Zeitschr. f. klin. Med.*, 1900, Nos. 3 and 4.

examination showed a moderate enlargement of the jugular glands, and a slight enlargement of the spleen, as well as lymphomata in the liver. The red marrow was normal to the naked eye, but microscopically showed lymphadenoid transformation. The second case was in a man of fifty-nine years, in whom the blood-count was 1,025,000 red corpuscles, 41,250 leukocytes, and 36 per cent. hemoglobin. The differential count was 4.25 per cent. polynuclear, 3.4 per cent. large lymphocytes, 91.5 per cent. small lymphocytes, and 0.8 per cent. eosinophile cells. There was much irregularity in the size of the red corpuscles and a small number of normoblasts were seen. Later the number of white corpuscles in the blood increased. The postmortem examination showed no enlargement of any of the lymphatic glands. The marrow of the ribs was of a pale flesh color and contained only small (typic) lymphocytes. There was lymphocytic infiltration of the periportal connective tissue of the liver.

Pappenheim does not regard these as instances of primary disease of the blood and secondary alteration of the marrow, but as primary disease of the marrow, causing the increased number of lymphocytes in the blood.

Dorothy Reed[1] has published a very careful study of a case of acute lymphatic leukemia, in which she claims to have proved conclusively that there was a "lymphocytosis arising from proliferation of lymphoid cells in the bone-marrow, and death occurring before any other organ in the body showed involvement." She quotes the opinions of Walz,[2] Pappenheim,[3] and Bradenburg,[4] that the bone-marrow in every case of leukemia is the starting-point of the disease, and states her own belief that "acute leukemia, whether lymphoid or myelocytic, is due to changes in the bone-marrow, the other organs being involved, if at all, secondarily."

Kelly,[5] in an article on acute lymphocytic leukemia, strongly supports the view that lymphocytic leukemia may have a purely myelogenous origin. In the first place he points out the fact that the bone-marrow is unquestionably to be included among the lymphoid structures of the body, and reaches the natural inference that it can therefore make lymphocytes. These lymphocytes, or, at all events, cells not to be distinguished in any way from the lymphocytes of the lymph glands and circulating blood, are unquestionably formed in the bone-marrow. He refers to the cases of acute lymphocytic leukemia without enlarge-

[1] *Amer. Jour. of Med. Sci.*, Oct., 1902.

[2] *Arbeit. aus dem Path. Inst. Tübingen*, 1899, Bd. ii., p. 1.

[3] *Zeit. f. klin. Med.*, 1900, p. 171

[4] *Charité Annalen*, 1900.

[5] *Trans. Assoc. of Amer. Phys.*, 1903.

ment of the lymph glands reported by Pappenheim,[1] Walz,[2] Reed,[3] Michaelis and Wolff,[4] Hirschlaff,[5] Körmöczi,[6] and Spencer,[7] Hayem and Bensaude.[8] Buchanan,[9] Dennig,[10] Pineles,[11] Politzer,[12] and Rosenfeld,[13] all of whom describe cases of acute lymphatic leukemia in which there was involvement of the bone-marrow alone. In such cases the short duration of the disease may be the explanation of the failure of involvement of other lymphatic structures. Such a view, of course, presupposes the bone-marrow origin of lymphatic leukemia. Kelly reports an instance of the same sort which furnished the basis for his paper. His deduction from these facts seems to the editor entirely justified. "In these cases, inasmuch as the blood contained large numbers of lymphocytes—in some cases enormous numbers—1 of the editor's cases revealing 551,319 lymphocytes to the cubic millimeter of blood; as the lymph glands, both macroscopically and microscopically, in some cases showed no deviations from the normal, in other cases but slight deviations; and as the bone-marrow revealed lymphadenoid metamorphosis in all cases in which it was carefully studied, the very obvious inference is to attribute the formation of the enormous numbers of lymphocytes to the diseased bone-marrow. It is not necessary, however, to believe that these lymphocytes are formed only in the bone-marrow, although it is likely that in most of the cases of lymphocytic leukemia the great majority of the circulating lymphocytes—in some of the cases all of the circulating lymphocytes—are formed in the bone-marrow. We are inclined to believe that they may be developed from any of the lymphoid tissues of the body that present the requisite alterations, such as the lymph glands, the other lymphoid nodes, as in the intestines, the thymus, and even the so-called metastases." Reference will be made to cases of acute myelogenic leukemia in another place.—ED.]

[1] *Zeitschr. f. klin. Med.*, 1902, vol. xlvi., p. 216.

[2] *Centralbl. f. allg. Path.*, 1901, vol. xii., p. 967.

[3] *Amer. Jour. Med. Sci.*, 1902, vol. cxxiv., p. 653.

[4] *Deutsch. med. Woch.*, 1901, vol. xxxvii., p. 651; *Virchow's Archiv*, 1902, vol. clxvii., p. 151; *Zeitschr. f. klin. Med.*, 1902, vol. xiv., p. 385.

[5] *Centralbl. f. inn. Med.*, 1898, vol. xix., p. 837.

[6] *Deutsch. med. Woch.*, 1899, vol. xxv., p. 238.

[7] *Lancet*, 1900, vol. i., p. 926.

[8] *La Medecin Moderne*, 1903, vol. xiv., p. 56.

[9] *Jour. of Bacteriology*, 1897, p. 242.

[10] *Münch. med. Woch.*, 1900, No. 38.

[11] *Wien. klin. Rund.*, 1899, p. 725.

[12] *Ibid.*, 1899, p. 197.

[13] *Zeitschr. f. klin. Med.*, 1901, Bd. 42.

SYMPTOMS AND COURSE.

Acute lymphatic leukemia is a disease lasting only a few days to several weeks, or exceptionally several months. It is frequently associated with fever and runs its course to death similarly to an acute infectious disease with asthenia and other general symptoms.

Descriptions of cases have become frequent since Ebstein's definition of the disease. Some observers (A. Fränkel, Bradford and Shaw) have described whole series of cases in the course of a few years, which would seem to indicate that all the cases of this disease by no means become generally known—whether it is that they are not published or are not recognized. The frequency of the affection is therefore probably much greater than the number of published cases would denote. Consequently, statistics in this regard are of little value. Among the cases described, almost two-thirds were in males. Children are attacked with relative frequency. The limits of age begin with birth (Pollmann[1]) and end with seventy-three years (Pineles). By far the greater number of patients were under forty.

[McCrae[2] has collected 13 cases of acute leukemia in the first decade of life. Of these, 11 were males. In 8 cases there was fever; in 4 general glandular enlargement; in 5, enlargement of the cervical glands alone; in 2, no enlargement; and in 2, no record regarding the glands. In all, the spleen was enlarged. The liver was enlarged in 3, and in 2 the size was not noted. There was a continuous increase in the proportion of the leukocytes, but not at any stage an increase of polymorphonuclear cells, as Reimann observed.—ED.]

The **onset** of acute lymphatic leukemia may be either sudden or insidious. In many cases the patient feels entirely well till the disease is at its height, and then the symptoms come on so suddenly that the first indication of illness occurs almost simultaneously with the taking to bed. In other cases general symptoms exist previously for days or weeks and may be considered as prodromes, though they are probably the result of the blood-disease. More accurate investigations of this primary stage, with attention directed to the origin of the blood-changes, though of the greatest importance, are entirely wanting, for there is nothing at that period to point to the severity or seat of the disease.

It is also very probable that in the cases with sudden onset of severe

[1] Whether fetal leukemia, which terminates with the intra-uterine death of the child and its premature expulsion, is to be reckoned in this category, and whether in this case the disease is at all comparable with the leukemia of adults, can not be concluded from the descriptions (Sänger, Klebs, Eppinger) at hand.

[2] *Johns Hopkins Hospital Bull.*, May, 1900.

symptoms the actual beginning of the disease must be referred to some time before, and that in the meantime the disease progressed without symptoms or, at least, unnoticed. [It is probable that some recorded cases were instances of chronic leukemia terminating acutely. E. Hirtz and M. Labbe[1] record a case of acute leukemia, of nine weeks' duration, in which there was an obscure nasal infection. They regarded the case as one of chronic leukemia terminating in a fatal septicemia. Bacterial emboli were found in the spleen and bone-marrow.—Ed.] Then, too, the blood-picture of lymphatic leukemia has been found in the acute cases at the first examination, even when this was undertaken very early. In fact, during complete absence of the subjective symptoms of disease a high degree of leukemia has been found after a large hemorrhage had called attention to a possible blood-disease (Theodor).

On the other hand we have accurate investigations of the blood in a few cases before the appearance of the leukemic blood-picture, which allows the onset of the outspoken disease to be determined with absolute certainty. In these cases the patients came under observation for some other affection, usually of a severe anemic nature, though this is not to be identified with the previously mentioned prodromes of acute leukemia.

[Reimann[2] records a case of acute leukemia in a girl of nine years, in whom the symptoms antedated the characteristic changes in the blood. At first there were indefinite symptoms; then hemorrhages, and a purpuric eruption, leukocytosis, enlargement of the liver, spleen, and lymphatic glands followed. There was at first an increase in polymorphonuclear elements. Later the lymphocytes increased and there was slight eosinophilia. It is of interest to note that the autopsy in this case showed an enlarged thymus gland as the most conspicuous feature. The early predominance of polymorphonuclear elements may have been the direct result of the hemorrhages.—Ed.]

The first symptoms, which sometimes precede the disease by many weeks, consist in general weakness, pain in the head and neck, dyspnea, pressure on the chest, a heaviness of the limbs, and other vague symptoms of a threatening disease (vertigo, feverishness). Sometimes the localization of these prodromes points to a blood-disease. Thus, several cases are reported which began with pains in the region of the spleen, others which set in like an acute articular rheumatism with swelling of the joints (A. Fränkel). Very frequently a pale puffiness of the face is noticeable; associated with this we not rarely have epistaxis and hemorrhages, and inflammatory processes of the mucous membrane of the

[1] *Gaz. des Hôp.*, May 16, 1900. [2] *Wien. klin. Woch.*, Sept. 28, 1899.

mouth, especially of the gums and throat (particularly the pnaryngeal tonsil) (Bradford and Shaw).

While these general symptoms differ in no way from those of other rapidly developing diseases, several peculiarities are to be mentioned which accurately characterize acute leukemia, or at least point to the diagnosis of a severe affection of the blood.

The gross signs of **swelling of the lymphatic structures:** lymph glands, spleen, sometimes the lymphatic structures of the mouth (especially the tonsils).

Enlargement of the **lymph glands** is almost never entirely wanting. The degree of enlargement varies, but never reaches the marked condition seen in chronic lymphatic leukemia. In several cases the largest glands were not more than hazel-nut size. Sometimes the enlargement is so insignificant that only toward the fatal termination are a few slightly enlarged cervical glands perceived. In fact, sometimes the glands are found to be larger than normal only at the autopsy. On the other hand, the swelling may disappear toward the end, simultaneously either with an increase (Gilbert and Weil, Green) or decrease in the lymphemia (see p. 561). In the majority of cases the most marked swelling, both at the beginning and in the course of the disease, is seen in the cervical glands, and it is here sometimes confined to one side. Yet rarely do we meet marked differences in the appearance of the different groups of glands, such as are frequently seen in chronic lymphemia and are the rule in pseudoleukemia. The glands are usually slightly, or not at all, sensitive (though marked tenderness has been observed) and are readily movable against one another and between the underlying and overlying soft parts. When the glands are painful, and especially when they are run together, we must not be too hasty in attributing a leukemic cause to them, since frequently a local irritation producing simple inflammatory swelling may be found, especially in disease of the mouth (Ebstein). The consistence of the glands is usually hard, and only rarely has an almost diffluent softness been observed.

The **spleen** is of normal size in less than one-third of the cases (Fussell, Jopson and Taylor). The enlargement usually seen is not as a rule considerable, yet immense spleens have been described, especially in children (Eichhorst, Müller, Theodor). A rapid enlargement during the short course of the disease is sometimes more evident in the spleen than in the lymph glands. The organ, then increasing from day to day, takes up the whole left side of the abdomen. It may be seen through the abdominal wall as a superficial, rounded, limited protuber-

ance, and sometimes (in the emaciated) is so evident that the boundaries may be determined by the eye. In the same way the hard tumor, regularly enlarged in all its diameters, with its sharp, well-defined border and evident incisuræ on the anterior border, is readily palpated. The borders are sometimes palpable around the whole spleen, with the exception of a small part of its summit—on account of the organ sinking from its site of attachment, after the fashion of a wandering spleen.

The **pharyngeal tonsils** are enlarged in about half the cases. Any connection with the degree of swelling in the cervical glands has not been determined, though it has sometimes been noticed that the most marked swelling in the cervical glands was on the same side as that of the tonsillar enlargement (Bradford and Shaw, Case 3). Children seem especially, though not exclusively, predisposed to the enlargement of the tonsils. The appearance is either of simple enlargement or of enlargement with hemorrhage into the tissue. Not rarely the tonsils are covered with a necrotic, diphtheric or hemorrhagic exudate.

Hemorrhages.—The most striking and characteristic clinical symptoms of acute leukemia are presented by the hemorrhages and their sequelæ. We refer here especially to the hemorrhages into the skin, the visible mucous membranes and the posterior eye-ground; further, the hemorrhages in the interior of the body—that is, those that are recognizable during life by their clinical results, as of the intestine, the bladder, the brain, and the labyrinth of the ear.

The skin hemorrhages occur as petechiæ on the buttocks and the extremities without regular localization or predilection. Their size is usually small, about that of the head of a pin, though very extensive extravasations also occur. Their further course is that of ordinary petechiæ—rapid disappearance, leaving behind a pigmentation with blood-coloring matter. Sometimes large and deep *necroses of the skin* arise, which spread rapidly and show not the slightest tendency to heal. Their origin is sometimes due to subnutrition of the lymphomatous infiltrated tissue in which the hemorrhage arose, again (directly) to small traumas like decubitus. That the skin in cases of acute leukemia is extremely sensitive to the slightest injuries, and that it possesses scarcely any power toward regeneration of defects, is evidenced by the foudroyant necrosis of the skin of the leg—following the application of a vesicant (Leube and Fleischer).

In the *mouth* the small hemorrhages are found either with an apparently intact surrounding or on a part of the mucous membrane changed by swelling or necrosis and ulceration. Their site of predilection is especially the gums, then the palate, the mucous membrane of the cheeks,

the throat and the nose. The simple petechiæ of the mouth and nose have no serious significance so long as the mucous membrane itself remains intact. Yet the erosions of even relatively small vessels may become dangerous if the mucous membrane is swollen and necrotic, and any contact, no matter how slight, may give rise to severe and long-continued hemorrhage. Severe hemorrhages may break through the mucous membrane, which is never absolutely sound at the site of rupture of the vessel, and lead to dangerous losses of blood (especially from the nose). Necroses and ulcerations arise at the site of the hemorrhage even more frequently than on the skin. These are often small, but again may be large and noma-like and rapidly destroy the mucous membrane of the cheeks.

Hemorrhages of the *posterior eye-ground* are found in almost all cases. They appear as smaller or larger foci, sometimes with a white center and are often surrounded by a clouding of the retina. This delicate veil-like clouding of the retina around the hemorrhage, associated with a more marked dilation of the veins than the arteries (Elschnig), is quite characteristic of leukemia; yet these fine clinical characteristics are often not sufficiently evident to allow a positive differentiation from other severe anemias.

As we shall see in the discussion of the anatomic changes, the very frequent hemorrhages into the *brain* and its membranes rarely produce symptoms corresponding to the extent of the lesions. In cases of hemorrhage from the hemispheres into the ventricles, hemiplegias have been observed; in widespread hemorrhages into many large foci, only general unconsciousness (A. Fränkel). These hemorrhages are survived only a few hours to several days and are almost always to be regarded as the immediate cause of death.

Paralyses of the peripheral *cerebral nerves* (branches of the facial and auditory), which have been several times noted, were discovered at the autopsy to be due in part to hemorrhages into their substance (Eichhorst, Schwabach). Affection of the auditory nerve and of the internal ear not rarely produces, besides deafness, which sometimes occurs suddenly, the well-known picture of Ménière's disease (Schwabach).

Hemorrhages from the *intestine*, the *urethra*, and the *vagina* are not rare and occasionally become the direct cause of death, like those from the mouth and nose. They are the result of rupture of vessels in the corresponding organs. We will discuss their seat and manner of origin, which are often of clinical importance, more precisely in the section on Pathology. Westphal describes a severe hemorrhage after puncture of the spleen by a fine cannula.

In addition to hemorrhages we find in a series of cases marked **swelling and ulceration** of the mucous membranes, especially of the mouth and throat, on account of their exposure to traumas. These are frequently the result of the breaking down of the foci of previous hemorrhage; yet again they arise in apparently healthy tissue, which, however, always shows marked microscopic changes (lymphomatous infiltration). These necroses of the mucosa, when they occur (according to Nobel, in 70 per cent. of the cases), constitute one of the most characteristic symptoms of acute leukemia, as they are common to but few other diseases, and consequently often suggest the correct diagnosis (a point insisted on especially by Bradford and Shaw). The site of predilection of these lesions is particularly the gums and the lips, then the palate, the uvula, the mucous membrane of the cheeks and the tongue. Sometimes, too, the nose and the entrance of the larynx, together with the epiglottis, are affected.

At first the lesion consists of a moderately hard swelling (infiltration with lymphocytes) under the sound mucous membrane. The gums are pushed outward to the edge of the teeth; in fact, the teeth may be completely hidden by the swelling. On account of the slight traumas constantly occurring in the mouth, inflammatory excitants are forced into the distended, thin, readily injured mucous membrane and produce here and there necroses. Mouth breathing, coming on usually as a result of occlusion of the nose, aids in the drying up of the buccal mucous membrane and makes way for the entrance of bacteria. The result is sometimes a diphtheric condition, again ulceration of the mucous membrane. The ichorous destruction of this dead mass produces the most fetid and disgusting odor of the exhaled breath. There is a continual flow of saliva. The teeth sit loosely imbedded in the spongy remains of the mucous membrane. Every touch produces hemorrhage, making a condition completely identical with that characteristic of scorbutus.[1]

The symptom which has given the disease its name and which constitutes the only positive diagnostic sign of leukemia is the **increase of white blood-corpuscles in the circulating blood.** The absolute number may increase to more than one-half a million in the cubic millimeter. Since a considerable decrease of red blood-cor-

[1] According to the predominant development of one of these three symptoms, Gilbert and Weil differentiate three clinical forms of acute leukemia:

(1) Typic acute leukemia, in which the swelling of the lymphatic structures stands out most prominently; (2) the hemorrhagic form, the principal characteristics of which are the hemorrhages; (3) the pseudoscorbutic form with hemorrhages and ulceration of the mucous membrane of the mouth and the nose.

puscles not rarely occurs at the same time, we find occasionally proportions of whites to reds of 1 : 3 or even 1 : 2. Still, the increase in leukocytes is usually not so great, and proportions of about 1 : 10 or 1 : 20 are more frequent.

In this leukocytosis the polynuclear neutrophiles constitute only a small percentage, being, at the most, normal in number, though usually diminished. Eosinophiles are rare, being almost always considerably below 1 per cent.; though in isolated cases over this amount (Bradford and Shaw, 1.6 per cent.). Only rarely is a small percentage of neutrophile myelocytes found (0.4 and 0.6 per cent. in 2 of Bradford and Shaw's cases). If the case described by Bloch and Hirschfeld, with 10.26 per cent. myelocytes, is to be reckoned with leukemia (as these writers aver), and not to anaemia infantium pseudoleukaemica, it represents the highest known maximum. We have tabulated here a few cases from the literature which present exact counts :

	White.	Red.	W. : R.	Lymphocytes. Small: per ct.	Lymphocytes. Large: per ct.	Myelocytes: per ct.	Eosinophiles: per ct.	Polynuclear neutrophiles: per ct.	Hemoglobin: per ct.
T. McCrae	26,000	1,700,000	1 : 65	87	2	1 ex.	1	. .	85
Kühnau	120,000	2,500,000	1 : 25	85	10	. .	5		
Fussell, Jopson, and Taylor	184,000	800,000	1 : 6	88.84	5.48	. .	. .	1.52	
Fussell, Jopson, and Taylor	362,000	1,273,000	1 : 35	79.37	5.54	. .	0.09	11	32
Gilbert and Weil.	22,010 to 46,400	4,500,000 to 1,840,000	1 : 205 to 1 : 39	60; 100		0	. .	0	
Körmöczy	6,000 to 107,000	2,300,000 to 1,600,000	1 : 383 to 1 : 15	10; 95	65	. .	5		30 to 20
Bradford and Shaw	34,500 to 68,000	2,250,000 to 1,500,000	1 : 72 to 1 : 22	12.2 to 13.4	61.8 to 64.3	0	26 to 22.3		26
Bradford and Shaw	74,000 to 280,000	2,500,000 to 2,000,000	1 : 33 to 1 : 7	6.9	90.4	0.6	1.6	0.5	40 to 30
Bradford and Shaw.	. .	. .	. .	0.88	98.49	0.4	0.23	0	
Hirschlaff	43,600 to 240,000	960,000	1 : 22 to 1 : 4	90		. .	. .	. .	20 to 15
Pineles	550,000	3,500,000	1 : 36	96					
Brandenburg	29,200 to 92,000	4,100,000 to 2,000,000	1 : 140 to 1 : 21	72–9		1	2	25 to 4	76 to 63

The increase, therefore, affects quite exclusively the *lymphocytes.*

The appearance of these cells has been minutely described by Ehrlich and Lazarus in the former sections of this volume. They are mono-

nuclear cells, varying from one to two or three times the size of a red blood-corpuscle. They are differentiated principally by their size, and the two extremes are designated by the names small and large lymphocytes, though between these two every form and size are found.

They are mononuclear. The nucleus lies centrally, is round, sharply limited, and stains in the dry preparation equally well with all nuclear stains. The smaller the lymphocyte, the darker the nucleus. In the nuclei of the small lymphocytes we find one (or two) round, sharply circumscribed clear spots, the nucleoli. These are seen especially well in fresh preparations after the addition of a weak acetic-acid solution. The nuclei of the large lymphocytes frequently show a larger number of clear spots.

In sections hardened by bichlorid of mercury the small lymphocytes especially show a very evident nuclear structure consisting of 2 to 3 chromatin masses, situated centrally, and 5 to 10 grouped about the border. All these dark granules are joined together by a moderately rough network of chromatin threads which is denser the smaller the nucleus, and the reverse.

The nucleus is entirely surrounded by protoplasm, though it may lie a little excentrically. The protoplasmic structure is usually not very clear, either in dry preparations or in sections. Frequently it is stained regularly by the basic anilin dyes (basophilic, and possibly even more so than the nucleus), though again it appears as granules, and sometimes as a sort of irregular honeycomb structure, which in the best examples is represented by a loose delicate network.

In acute lymphatic leukemia the small lymphocytes usually stand in the background, allowing the picture to be dominated by the larger lymphocytes. The latter are characterized by a large faintly and regularly stained nucleus, filling almost the entire cell, and a small amount of protoplasm which is devoid of eosinophile, neutrophile, or mast-cell granules, and takes the basic stains better than the acid and sometimes shows a sort of fine basophile granulation.

These large lymphocytes are identical with the forms described as premature cells, unripe cells, or marrow cells (Markzellen). These names, the last of which indicates their origin from the markedly hyperplastic bone-marrow, play a considerable rôle in the misunderstanding of leukemia. The name marrow cell is especially misleading, and none the less so on account of confusion with Ehrlich's neutrophile myelocyte, the forerunner of the ordinary polynuclear white blood-corpuscle. Moreover, this name has but little justification, since the number of these cells that originate in the bone-marrow is normally

EXPLANATION OF PLATE III.

FIG. 1.—BLOOD IN ACUTE LEUKEMIA.

Besides red corpuscles, the chief feature is large lymphocytes whose nuclei show a delicate network with large clear areas. *a*, Small lymphocytes with dark-blue, coarsely granular nuclear framework; *b*, polynuclear leukocyte.

From a specimen fixed with heat and stained with hematoxylin and aqueous eosin solution (Zeiss, Oc. II. Hom. Immer. $\frac{1}{12}$).

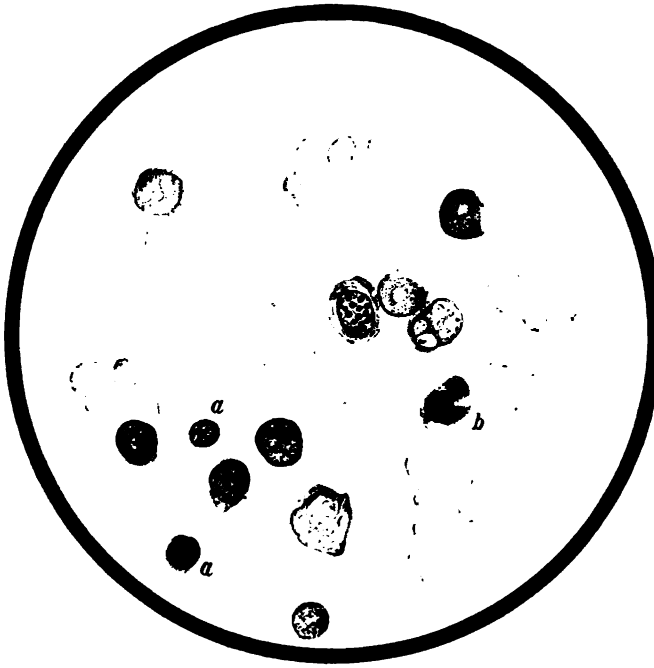
FIG. 2.—BLOOD IN CHRONIC LYMPHATIC LEUKEMIA.

Besides red corpuscles, the chief feature is small lymphocytes with a narrow border of basophil (dark-violet blue) protoplasm. *a*, Large lymphocyte with basophil protoplasm; *b*, polynuclear lymphocyte.

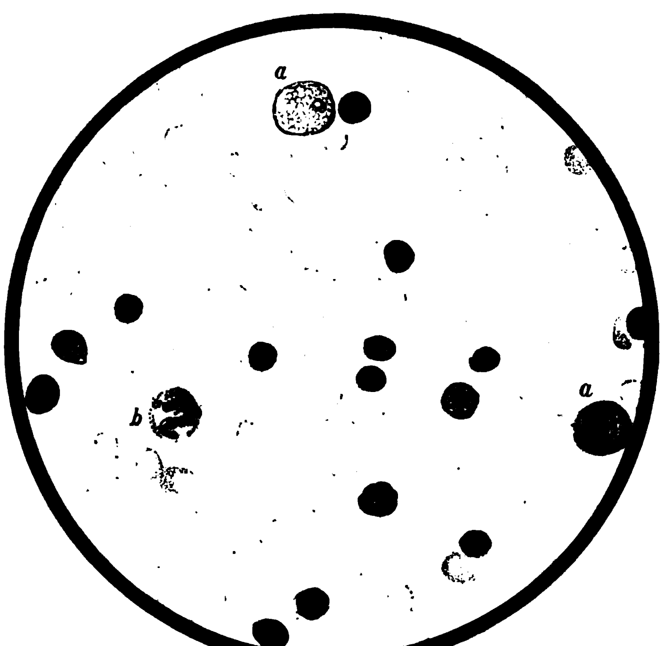
From a preparation fixed with formalin and stained with aqueous solution of eosin and aqueous solution of methyl blue (Zeiss, Oc. II. Hom. Immer. $\frac{1}{12}$).

PLATE III.

1



2



very small, while all the lymphatic structures of the body contain them. The correspondence of these "marrow cells" of acute lymphatic leukemia with Ehrlich's large lymphocytes has, since Fraenkel's work, been generally granted. There is no reasonable ground for the assumption that the large cells answering this description and arising from the bone-marrow (which Benda comprised under the name myelogonies) are to be differentiated from the exactly similar ones originating from the lymphatic apparatus (Benda's lymphogonies).

Deviations from the normal appearance of the lymphocytes are rare, and when they occur they affect exclusively the nucleus. Such nuclei are indented, lobulated, almost divided or even broken up into two or more pieces, though they are always distinguishable by their size, faint color, and irregularly plump shape from those of the polynuclear leukocytes. The protoplasm, too, is distinguished by its small amount and the absence of neutrophile granulations from that of the ordinary polynuclear leukocytes (see p. 587).

No definite rule can be stated for the proportion of large to small lymphocytes. There are cases in which the large form is almost exclusively present, and others in which it is almost wanting (Theodor). Nevertheless, as Fraenkel first stated, in acute leukemia the large cells, as a rule, predominate, while only a few isolated cases of chronic lymphatic leukemia with an exclusive increase in the large forms have been described.

The number of red blood-corpuscles is rarely normal, and, as a rule, fluctuates between 1,000,000 and 3,000,000 (see table, p. 555). The occurrence of small numbers of nucleated red blood-corpuscles may be considered the rule, large numbers extremely rare (in 1 case of Fussell, Jopson and Taylor 1 : 173).

The percentage of hemoglobin in the blood is always under 50.

The characteristic blood-picture (increase in lymphocytes) has been found, except in those few cases of acute lymphatic leukemia following severe anemia, at the beginning of the disease—that is, as soon as the clinical symptoms showed reason for the examination of the blood, or, in other words, as soon as the patient sought medical aid. When the alteration of the blood begins, and how it develops, is unknown in any typic case. The increase in the lymphocythemia during the course of the disease, however, has been frequently followed and has sometimes been found to be uncommonly rapid; for instance, in one case in five days there was an alteration of the ratio of whites to reds from 1 : 35 to 1 : 7, the red blood-corpuscles remaining practically stationary (2,500,000 to 2,000,000), the increase in whites being from 74,000 to

280,000; in another case, in eight days an alteration of from 1 : 43 to 1 : 25 was noted, with a decrease of red blood-corpuscles from 2,500,000 to 1,500,000, the increase in whites being from 34,500 to 68,000 (Bradford and Shaw).

[Hitschmann and Lehndorff[1] describe a case of leukemia with severe megaloblastic anemia in a patient of thirty-four, who had a rapidly developing anemia that advanced in the course of three weeks to such a degree that the number of red corpuscles was only 724,000. The proportion of red to white fell from 200 : 1 to 21 : 1, and finally, just before death, from 5 : 1. The number of white cells, however, was not greatly increased, the maximum being 35,000. The mononuclear cells numbered 96 per cent., of which 76.6 per cent. were large non-granular forms. Among the mononuclear cells were numerous non-granular basophile cells, such as occur only in the bone-marrow. The nucleated red corpuscles, and especially megaloblasts, were present in large numbers.

The case is of interest as showing how a megaloblastic process in the bone-marrow may be secondary to other blood-conditions.—Ed.]

In a very few cases patients were already under observation on account of another disease, as severe anemia (Litten, Waldstein, Gottlieb, Körmöczy) or pseudoleukemia (Mosler, Senator, Martin, and Mathewson), when the unsuspicious blood-picture changed, two or three or four days before death, into a marked leukemic one (leukemia acutissima). Still, in these cases the origin and course were so rapid (Litten, Hilbert, Fuchs) that no opportunity was presented of observing the mode of development.

GENERAL SYMPTOMS.

Besides these more or less characteristic symptoms, there are a number which acute leukemia has in common with other fatal asthenic diseases.

The most striking are the wax-like yellow to gray **pallor of the skin** of the face and body and the puffiness of the face. Edema occurs, but is not frequent; more often we find an increased diuresis, so that the daily quantity of urine increases to even 4 L. and over. An accompanying albuminuria has been observed, but only rarely. Kühnau reports an acute hemorrhagic nephritis shortly before the fatal termination, yet, generally, inflammatory kidney changes are even more rare than the albuminuria would indicate. As already mentioned, hematuria dependent on hemorrhage into the urinary tract is not rare.

[1] *Zeitschr. f. Heilkunde*, 1903, No. 5.

Priapism was found several times (Craig), and in 1 case (Ward) could be referred to a thrombosis of the corpora cavernosa (following occlusion of a vein), similarly to the process described by Kast in myeloid leukemia.

The **liver** is frequently enlarged, in fact almost regularly in the leukemia of children. Still, it seldom gives rise to icterus, and even the occasionally appearing green color of the urine is not referable to bile coloring-matter, but to a peculiar green substance which we will discuss more at length when speaking of chloroma.

As a result of the hemorrhages from all the body cavities and into all the organs, and of the not infrequent diarrhea and defective absorption, emaciation is extreme. It finds its highest expression in the nitrogen loss, which has amounted to over 20 gm. daily (Magnus-Levy).

The increased **excretion of uric acid** is the result of a special peculiarity of metabolism. It was found as uric acid or urates in the urine, or as uric acid infarcts in the kidneys, in the first cases of leukemia observed, and is especially marked in the acute exacerbations of leukemia, and, therefore, in acute leukemia. In the beginning this increase was referred to the fever present at the time (Mosler and Körner). Later, an undoubted connection was found with an increased destruction of nuclein, which from histologic observation (Gumprecht, Krönig) and experimental investigation (Schreiber and Zaudy, Kühnau and Weiss) may be regarded as the result of the breaking up of white blood-corpuscles. Still we must remember that this destruction is not always so great as the quantity of uric acid excreted would indicate, and there is possibly another factor not yet clearly understood (Magnus-Levy). Further, uric acid may arise from bodies introduced with the food (Minkowski). The sedimentation of uric acid in the urine is not positive evidence of increased excretion, for under certain circumstances small amounts are sometimes precipitated, while again much larger quantities remain in solution (Magnus-Levy). This increase in uric acid in the urine, though frequent, is not necessarily the rule. In 1 case of Fraenkel's it amounted to more than 12 gm. in forty hours. At the same time there was found, probably also as a result of the breaking up of nuclein, an increased excretion of phosphoric acid to over 15 gm. The fact that the quantity of uric acid excreted does not correspond to the used-up leukocytes gives reason for the assumption that the destruction of nuclein does not necessarily stop at the production of uric acid, but sometimes is further oxidized and only then excreted (Minkowski).

The **heart activity** is almost always increased. At autopsy endo-

carditic changes have been frequently found (Senator, Pollmann); in fact, it is on such a change that Senator bases the symptom of the centripetal venous pulse observed in one of his cases.

The **respiration** often presents no peculiarities. Still we occasionally find severe dyspnea from occlusion of the nose and throat by lymphomatous masses and a disgusting odor of the breath from necrosis of the gums, tongue, and mucous membrane of the cheeks. Sometimes the limitation of the chest space by lymphatic tumors (enlargement of the thymus or the mediastinal glands) produces considerable dyspnea. The *oxygen metabolism* seems to suffer no alteration. Among the accompanying affections of the respiratory organs, bronchial catarrh is almost constant.

Fever is frequently present and sometimes, especially toward the end of life, reaches high grades (40°–41° C.). On the other hand, cases have been observed showing a terminal drop of the temperature, which had been moderately high from the beginning. The curve of the fever is very irregular. Frequently it recalls the curve of typhoid, frequently, too, that of sepsis, provided it is not itself to be regarded as septic. Generally we have to do with an irregular, not exactly high, fever, and during the day complete apyrexia is not rare.

COURSE.

The body is able to resist all these influences but a short time. It is not long before a marked loss of strength develops, which only rarely gives way to a temporary improvement or relative eupnea. Generally the disease runs a rapid course to death. The **duration** never exceeds a few months, and all variations are found from a few days to longer periods. Ebstein gives, as the longest duration, 63 days; Gilbert and Weil, 112 days; yet, the course may be even somewhat slower and still correspond to the clinical picture of acute leukemia. As in other affections, the clinical course of the disease is of much greater significance than its duration, a fact that is readily supported by the foregoing observations.

Death, often hastened by the severe loss of blood, especially from the nose and mouth, occurs from marasmus or in coma.

[J. L. Miller and J. Hesse[1] report a case of acute leukemia in which death occurred from rupture of the spleen. The patient was a man aged twenty-four. In October, 1901, he consulted a physician on account of loss of appetite and severe abdominal pain, and was supposed to be suffering from acute gastritis. These symptoms recurred during

[1] *Amer. Medicine,* March 5, 1904.

five weeks, when he came under the care of the author. There was pain in various parts of the abdomen, above and below, as well as in, the lumbar region. His liver was enlarged and the spleen just palpable. The abdomen was uniformly distended by tympany. There was also pain along the crest of the ileum. Toward the end of November, 1901, the patient was moderately febrile and had marked anemia; epistaxis and bleeding from the gums now developed, while the lymphatic glands were enlarged. There was marked tenderness in various bones. The spleen had increased somewhat in size. At this time the number of leukocytes was 50,000; the red corpuscles, 2,800,000; the hemoglobin, 48 per cent. The differential count showed small lymphocytes 4 per cent., large mononuclear 84 per cent., eosinophiles 3 per cent., myelocytes 1 per cent., polymorphonuclear neutrophiles 8 per cent.; and also numerous nucleated red corpuscles, chiefly megaloblasts, many of which showed mytoses. On the day following this examination, in attempting to walk to the bath room he fainted and fell; later vomited bile-stained mucus, containing small clots of blood. Death occurred the next day. At the autopsy the spleen, which was 10 cm. by 15 cm., soft, pulpy in consistence, showed two tears about 3 cm. in length, extending deeply into the substance and coated with lymph. Also there was a small circular area of necrosis about 1½ cm. in diameter, the base and edges of which were coated with lymph. The bone-marrow of the ribs and sternum were reddish gray, and on histologic examination showed not a single granular cell.—ED.]

Sometimes the course is so altered by an added septic infection that all the evidences of leukemia disappear in a few days. This condition has been thoroughly studied, especially by Fraenkel in 2 cases, one of which succumbed to infection with the Staphylococcus albus, the other with the Bacterium coli. Under the temperature variations the spleen and lymph glands decrease to about normal size. At the same time the number of white blood-corpuscles in the circulation sinks to about normal. This diminution sometimes affects all varieties of leukocytes, both lymphocytes and polynuclear leukocytes, though the former to a greater extent; in other cases only the lymphocytic increase disappears, and its place is taken by a moderate polynuclear leukocytosis. Everything goes to prove that the diminution in leukocytes is to be referred to an enormous destruction of these cells and the excretion of their metabolic products, since the simultaneous decrease in size of the lymphatic structures can be explained in no other way.

PATHOLOGIC ANATOMY.

GROSS ANATOMY.

Hemorrhages.—The most widespread alterations are the hemorrhages found in the skin, the exposed mucous membranes, the retina, the serous membranes (pleura, peritoneum, pericardium), and the mucous membrane of the whole intestinal tract and urinary passages, particularly the pelvis of the kidney and the bladder. Not rarely, too, we find hemorrhages in the brain, which when small may give rise to no symptoms, but if located in the motor region, may produce hemiplegia or other paralyses.

The lymphatic accumulations in the internal organs are less striking than those ordinarily seen in chronic lymphemia. The **lymph glands** are invariably enlarged. The degree of swelling varies within wide limits, as we have shown in the clinical description. Their appearance is marrow-like, white, and their consistence hard, provided the tumors are not large. Smaller glands are usually reddish gray. Hemorrhage into the glandular substance is common, and, on account of its rarity under other circumstances, is quite characteristic. Retrogressive changes scarcely ever occur. The rare abscess formations are to be referred to secondary infection.

In the minority of cases the **spleen** is normal in size and appearance; usually a moderate enlargement is found. Only very rarely, and then almost exclusively in small children, is the tumor large, reaching sometimes the largest size observed in chronic leukemia. The color of the cut section is grayish red to brownish red, the follicles usually being enlarged, often sharply limited, though more frequently undefined and washed out. The consistence is commonly soft, sometimes almost diffluent. Infarcts showing a hard consistence are occasionally found, and apparently more frequently in these rarer cases (Gläser, Symes-Wadham).

The practically constant changes of the **bone-marrow** are especially striking. In the long tubular bones it is almost always transformed into a rich cellular marrow, which does not show the regular alteration found in chronic lymphatic leukemia. The metamorphosis usually affects the tubular bones throughout their whole extent, yet sometimes individual parts (*e. g.*, one-half of the femur diaphysis) are spared, and show a normal fat-marrow. The appearance is frequently deep red and of soft gelatinous consistence (raspberry or currant-jelly-like), more rarely grayish to red gray and firmer, like the marrow of chronic lymphemia. Greenish-yellow patches, resembling pus, some-

times occur and suggest the finding in chloroma. Irregularly distributed hemorrhages vary the color and make the picture more striking.

It is noteworthy that it is not only the marrow of young persons and the fat-marrow of adults that undergo this transformation, but it occurs even in that of old people, as can be seen from Pineles' case (a seventy-three-year-old woman).

The alteration of the marrow is most evident in the long tubular bones, where it appears to be most marked, while the normal red marrow of the short and flat bones is usually pale, or light brown to brick red in color.

Among the other lymphatic structures of the body, the most constant enlargement is seen in those of the intestine. A certain amount of **swelling of the tonsils** is almost always observed. This consists in an overgrowth of the lymphadenoid tissue, supplemented by hemorrhages. Not rarely, too, we find deep-seated necroses, the origin of which we will study more closely later.

Just as in the tonsils, swelling of all the other lymphatic structures of the **tongue, palate,** etc., occurs. Moreover, lymphadenoid nodes are sometimes observed in situations where normally none was especially noticeable, and they are, therefore, to be placed in the category with the scattered lymphomata generally (in the kidney, liver, etc.). For instance, Askanazy describes nodules extending into the musculature of the tongue, as well as others in the uvula. Among the most frequent seats of lymphatic deposits are the **gums,** especially of the lower incisors. The **pharynx** and **esophagus** seemingly rarely manifest lymphatic growths; in fact, hemorrhages appear to be the only sign of leukemic change in them.

In the **stomach** and **small** and **large intestines,** on the contrary, collections of lymphadenoid tissue are frequent. The situation of these nodules varies, in that in one case the stomach and large intestine, in another, the small intestine or even smaller sections of the tract, are alone or predominantly affected. Here, as in the mouth, there exists a tendency to superficial necrosis with the subsequent formation of ulcers surrounded by a marrow-like border, which when located at the sites of predilection of typhoid ulcers may give rise to serious diagnostic difficulties.

[In Dorothy Reed's case the prevertebral hemolymph nodes were found dark red in color, but not enlarged.—ED.]

Other lymphatic deposits are found now and then in all the organs of the body, especially in the large glands of the abdomen, as the **liver** and **kidneys.** The lymphomata found here are often so small

as to be unrecognizable to the naked eye. Yet even these very small microscopic collections of lymphocytes when widespread are capable of producing the picture of general swelling and hyperplasia. Postmortem the **thymus** is always present, and frequently in a condition of great enlargement (Reimann, Brandenburg), a fact which seems to be of importance on account of the evidence that this organ is the first storehouse of leukocytes, even before a place of formation exists elsewhere (Beard).

In addition to the alterations produced by the hemorrhages and the lymphatic deposits, we frequently find degenerative processes in the parenchymatous organs and sometimes even in the muscles and nerves.

A constant symptom is the disappearance of the subcutaneous fat. In like manner fatty metamorphoses of the heart muscle, sometimes reaching a high grade, are frequent. Parenchymatous hepatitis and fatty degeneration of the liver are rare, and acute hemorrhagic nephritis (Kühnau) is exceptional. Foci of degeneration have several times been found in the cerebral nerves, especially the branches of the facial and auditory. Hemorrhages into the eye may be considered the rule, and hemorrhages and lymphatic infiltration of the labyrinth and the tympanic cavity are frequent (Schwabach). As an occasional complication, we may mention endocarditis (Englisch, Pollmann, Senator, Cameron, and Sänger).

HISTOLOGIC ANATOMY.

The histology of the acute lymphatic deposits is absolutely uniform. In the peculiar lymphatic structures (lymph glands and follicles of the intestinal tract), as well as in the spleen, bone-marrow, and other organs, the leukemic cell accumulations consist of lymphocytes exactly similar to those in the circulating blood.

The histologic structure of the lymph glands alters considerably from the normal. The internal structure of the gland, so far as the differentiation of lymph vessels and the cell-producing parenchyma is concerned, is, to a certain extent, retained, but the cellular part exceeds by far the vascular stroma. In the arrangement of the cells the alteration is marked. While the normal gland shows only scattered foci of active cell proliferation here and there within the medulla (the so-called germinating centers), in acute leukemia the gland is transformed into a uniformly proliferating focus, which contains only a very small proportion of typic small lymphocytes at rest, and consists almost exclusively of large lymph cells in active mitosis (Benda's lymphogonies). In other words, the whole gland takes on the histologic character of the germinating center (Keimcentrum, Benda). There appears to be an

extremely lively discharge of lymphocytes into the blood, so that no collection of lymphocytes occurs in the depots surrounding the germinating centers from which normally the small lymphocytes are forced into the blood by simple centrifugal pressure. The slight overgrowth of the glands, in comparison with the rapid increase of lymphocytes in the blood, speaks likewise for this conclusion. The principal cells manufactured by the gland are large mononuclear forms with a very small amount of protoplasm. They resemble in every way the large lymphocytes already described. The nucleus stains faintly, but shows (especially with hematoxylin) a rough chromatic network. The protoplasm takes up the basic anilin dyes more or less, stains very feebly with acid dyes, and is composed of a loose honeycomb mesh, which sends out, here and there, jagged short projections.

The structure of the enlarged lymph follicles of the intestinal tract, and the so-called "metastatic" lymphomata located especially in the parenchymatous organs, though also in other places where no accumulations of lymphadenoid tissue are ordinarily seen, resembles exactly the structure of these glands. Histologic examination frequently shows that the lymphatic infiltration is far more extensive than would have been supposed from the naked-eye appearance.

In the mucous membranes the lymph nodules often extend quite to the epithelium above and to the musculature below. Moreover, they are composed of the same lymphocytes, frequently fully developed, as are found in the blood. These lymph-cell accumulations are located about the vessels and often within their walls. Their size varies from the smallest nodules to large tumors, visible to the naked eye.

These conditions are especially evident in the abdominal organs, particularly the liver, divided as it is by its vessels into so many sharply separated regions. In the liver the cell accumulation begins about the branches of the portal vein, therefore between the acini, where small lymphomata are built up. Still, here and there, even if not constantly, the lymph cells force themselves into the center of the liver lobule, and in this way produce an undefined boundary which has always been considered as an especial characteristic of leukemic tumors.

These lymphomata undergo secondary alterations referable partly to peculiarities of leukemia, partly to external agencies—in other words, to the two conditions mentioned before as peculiarities of this disease—namely, hemorrhage and ulceration.

Hemorrhage is frequent from even apparently healthy surfaces—for instance, the pale, non-swollen gums, the palate and all the other localities mentioned before. It is likewise quite as frequent in the

grossly altered lymphomatous tissue. The microscope shows both varieties to be due to the same cause, for wherever we find hemorrhage we find, too, an accumulation of lymphocytes about the vessel wall, from which we conclude that an injury to the vessel is first brought about by the lymphoma formation in its wall (Benda). No other alterations of the vessels that are readily capable of producing rupture are known. The direct cause of the hemorrhage must be sought in trauma in the widest sense of the term, the further influence of which on the altered tissue we will study later.

Necroses and Ulcerations.—According to their location, we differentiate two varieties: necroses of the mucous membrane and of the external skin. The former have been thoroughly described by Askanazy. Two forms are distinguished:

Superficial erosions at the site of a hemorrhage (described by Askanazy in the stomach). Since an infiltration with lymphocytes is usually found at the site of a hemorrhage, this variety of ulceration differs from the following only in that the hemorrhage injures the tissue still more and brings about a loss of the epithelial covering.

Ulceration at the site of an infiltration, seen with especial frequency in the mouth. Here we see the gums, according to Askanazy's splendid description, uniformly packed from the epithelium down to the periosteum with large mononuclear round cells, the vessels being filled with lymphocytes. The epithelium, thinned and desquamated, consists of cells loosely attached to one another, and is infiltrated with polynuclear pus cells (and eventually also with mast cells). In isolated places the tissue is necrosed throughout its whole extent. These spots frequently remain covered by epithelium and papillæ and lie sharply defined in the midst of the lymphocytic collections. The necrotic portion shows a diffuse staining, and is separated from the surrounding tissue by a zone of nuclear débris. The marginal parts are filled with bacteria.

These necroses are the result of slight mechanic injuries, such as are continually occurring in the mouth, and inflammatory excitants which gain entrance through the tense, partially defective epithelium. After the discharge of this surface necrosis an ulcer remains.

These ulcers, following necrosis of lymphadenoid tissue which, with the hemorrhages, constitute the characteristic peculiarity of acute leukemia, are located almost exclusively on the mucous membrane of the digestive tract and of the nasopharynx. They also occur in the lymphomata, arising from previously formed lymph nodules, like those in certain places in the mucosa; in fact, between these two varieties there is no particular difference, either in structure or in origin.

The mucous membranes of the mouth, especially of the gums, the cheeks, the soft palate and the uvula, exposed as they are to numerous injuries, are very frequently affected. Not at all rarely the ulcers extend over a large portion of the intestine, showing a special predilection for certain parts, though this varies in different cases—now a section of the small intestine suffering, again the large intestine.

Rarer than the ulceration of the mucous membrane, but by far more deep-seated, are the *necroses and ulcers of the skin.* They occur either at sites of previous cutaneous hemorrhage, especially on parts exposed to pressure (the buttock), or on parts subjected to gross mechanic injury, as by a vesicant (Leube and Fleischer), but also elsewhere on the body (the face). Following the rupture of the skin, extensive loss of substance takes place. Histologic investigations as to their mode of origin are yet wanting. From the analogy of ulceration elsewhere in leukemia, it is probable that the necrosis and ulceration develop in lymphatic deposits following hemorrhage. It is likewise possible that their origin is, to a certain extent, similar to that of the abscesses which Benda found as a result of secondary infection in the midst of lymphomata of the kidneys—in other words, the cause may really lie in an accidental injury.

The spleen presents almost the same appearance as the hyperplastic lymph glands. Its normal structure is more or less obliterated. The undefined borders of the Malpighian bodies are frequently noticeable, even to the naked eye, and become even more conspicuous under the microscope. The scraped preparation shows the different large mononuclear round cells usually in the same quantitative proportions as in the blood. Other elements (mast cells, neutrophile leukocytes) are scanty. On microscopic section the similarity with the lymph glands is very marked; the whole organ is packed with lymphocytes which are similar, both in shape and appearance, to those of the lymph glands. Only here and there do we find normal splenic parenchyma with evident follicles.

The bone-marrow is of much greater interest than the organs so far described; in fact, in its alteration the basis of the leukemia has often been sought.

Roughly speaking, the marrow is composed entirely of cell accumulations. Some of these cells are represented by the red blood-corpuscles and their advance stages, which are always present, yet these are of no special interest, since, apart from a possible diminution in number, they manifest no alteration, either in form or otherwise. The other cellular elements, on the contrary, are of the greatest importance. Fre-

quently only scanty numbers of the typic marrow elements, the neutrophile myelocytes, are found, while small and large lymphocytes, represented by mononuclear non-granular cells, typic in form and agreeing in every particular with the lymphocytes in the circulating blood, constitute practically the whole mass.

The changes in the marrow, therefore, as in the other organs, consist in a unique hyperplasia of the lymphocytes, which almost completely replace all the other tissue—in other words, we find an actual "lymphoid" marrow.

The functionating parenchyma of the bone-marrow remains a non-participant in the whole process till the cells are forced into it by mechanic pressure, just as in other organs—*e. g.*, the liver and kidney, the parenchymatous cells take no part in the proliferative process, though the lymphatic tissue may have penetrated between them. How small the number of remaining marrow cells (myelocytes, Ehrlich) can be is shown by the enumerations made with scrapings of the marrow (Bradford and Shaw). In 1 case these showed 0.2 per cent. of neutrophile polynuclear cells, 0.2 per cent. of myelocytes, and 99 per cent. of large and small lymphocytes. This metaplasia seems, in fact, to be the rule. Nevertheless, lesser grades occur, as is readily proved by the cases in which remnants of the normal fatty marrow may yet be seen. Further cases have been described (Benda) in which a uniform hyperplasia of all the leukocytic elements apparently took place, so that an increase of mononuclear neutrophile myelocytes was found, in addition to that of the lymphocytes.

The clinical expression of this alteration of the bone-marrow is found in the blood, since the diminution in the polynuclear neutrophile cells is to be attributed to the limitation of their site of manufacture in the bone-marrow. An organ producing normally red blood-corpuscles and polynuclear leukocytes becomes now a source of lymphocytes. Still, the function of whatever remains of the normal marrow tissue is not abrogated, as is evident from occasional suppuration, which always contains the typic constituents of pus—namely, the polynuclear neutrophile granular cells. In fact, in spite of its lessened number of myelocytes, there appears to be sometimes a peculiar pathologic washing-out of the bone-marrow, since in some cases a small percentage of neutrophile myelocytes (up to ½ per cent.) is found (Bradford and Shaw).

HISTOGENESIS.

Having studied the histology of the organic changes in acute leukemia, the question arises, How do the lymphomata and the blood-alterations originate? The fact that we have to do with a pure lymphocytic affection simplifies the matter considerably. As a matter of fact, there is only one point to settle—namely, whether the bone-marrow, which always participates, acts as the starting-point of the leukemia (Neumann), or whether we have to do with a regularly widespread tendency to hyperplasia of the lymphatic tissue (Ehrlich). In deciding this question we must remember that in all cases in which the bone-marrow alone seemed to show evident changes, the remaining lymphatic structure was not entirely intact. The very rapid increase in the lymphocytosis supports the conclusion that the failure of enlargement of the lymph glands and spleen is due only to the prompt discharge of the newly formed cells, and so the physiologic compensation which would be demonstrated in a swelling of the glands is prevented. The evidence from the histologic examination is sufficient to show that there is a decided increase in cellular formation in the lymph glands and the other lymphatic structures, even though they are not enlarged. As a matter of fact, no case has been impartially described which was purely "medullary." [In the light of more recent publications, this statement can not be accepted, even though newly formed elements in the lymphatic glands and spleen are discharged into the blood with great rapidity. Some evidence would surely remain.—ED.]

Moreover, on the whole, this question is of but little importance at the present time, since neither view adds anything to the explanation of the pathogenesis of leukemia.

The only important point is the fact that we are dealing with lymphocytes. From our knowledge of these cells is derived all that we know about the histogenesis of the disease. First, the lymphocytes are not wandering cells and stand in no relationship to the wandering cells. They are unable to leave the vessels by their own power, and are likewise unable to collect of their own accord about particular sites. They escape from the circulation into the tissues only mechanically—*i. e.*, only after injury to the vessel wall. Moreover, it has not been proved that these extravasated cells continue to live and proliferate so as to play any considerable rôle in the lymphomatous tissue formation (after the fashion of metastases). On the contrary, we have the best of grounds for believing that the accumulations of lymphocytes in every location are the result of cell proliferation in previously existing small lymphatic nodules found even in many normal organs (Ribbert), and

that all these lymphomata, no matter where situated, whether in glands, the spleen, the bone-marrow, the liver, the kidneys, the skin, etc., discharge cells into the blood, while the reverse—namely, the deposition of lymphomatous masses from the blood, does not occur (Pinkus).

We are unable here to go into all the evidence for this theory, since the greater part is taken not from acute leukemia, but partly from chronic lymphatic leukemia and partly from the ordinary inflammatory round-cell infiltration. We will mention only the fact, which is easily confirmed in these cases, that the development of lymphomata takes place *in situ*, as is proved by the numerous mitoses not rarely seen.

Yet, in spite of this mitotic increase, we find almost unexceptionally only very small collections of lymph cells, though the duration of the disease might readily lead us to expect the reverse. Still, as the small size of the lymph glands is explained by the rapid discharge of their elements into the blood, so we can explain the small size of the multiple lymphomata. Moreover, from this discharge of lymph cells from all parts of the body we have the simplest explanation of the not infrequent rapid increase of lymphocytes in the blood.

The transition of lymphocytes into polynuclear leukocytes has so far never been observed, and Benda's assumption of such a transition from the occurrence of abscesses made up of polynuclear leukocytes, in the midst of renal lymphomata, has long since been controverted by the demonstration of constant polynuclear suppuration, even in the most severe cases of lymphemia.

ETIOLOGY.

The whole picture and the rapid incurable course of acute leukemia give the impression of an acute infectious disease. Moreover, the unique pathologico-anatomic finding, the accumulations of lymphocytes, which serves as a base for all the other appearances, is not against such an assumption. From its first description, therefore, proofs have been sought for this view, and isolated findings of bacteria seemed to support it. Yet, on critical examination, the proofs have always been found insufficient. The only fact demanding earnest consideration is the frequently quoted observation of Obrastzow, who saw the disease break out in a nurse a short time after caring for a fatal case of acute leukemia. Still, in this case the possibility of an accidental coincidence can not be excluded, since, with the exception of a few instances in families, referred to under Pseudoleukemia (p. 624), the occurrence has never been repeated, even after the closest contact. Moreover, in Askanazy's case in a pregnant woman, the child was not

affected.[1] Further, the occurrence of acute leukemia in isolated cases in the newborn speaks against infection, although, apart from the possibility of infection *intra partum*, there is always the question, Whether, with the liability of the leukocytic apparatus in the newborn, the alterations in the blood and organs have the same significance as in adults?

Recently, the question of the excitant and the manner of infection in leukemia seemed to be decided by Löwit. We will go into his work more in detail in chronic leukemia, and here only refer to what applies to acute leukemia. Löwit believes that he is able to demonstrate, by a particular staining method, peculiar characteristic forms in the lymphocytes (usually in their nuclei), which he describes as unicellular animal organisms or hemamebæ. They are found more frequently in the blood-making organs (lymph glands, spleen, bone-marrow) than in the blood itself, and usually in fully virile—in fact, frequently mitotic—cells, while they are wanting in those which show degeneration.

Thus we stand at the beginning of our knowledge in the investigation of the excitant of acute leukemia. Even in relation to the predisposing factors, our knowledge is still quite limited. It is more frequently seen in youth and in the male sex (see p. 549), a fact which we will recur to in discussing chloroma. Lymphatic leukemia in children seems usually to run a more rapid course. As a rule, no particular injurious influence can be demonstrated. The patients are usually in good circumstances and are not exposed to overwork. Various things have been mentioned as preceding the acute onset of acute leukemia; for instance, once (as in scorbutus) a diet devoid of vegetables (Bradford and Shaw); and several times severe anemia, debilitating nursing, and influenza (Litten).

It is possible that in these cases the exciting factors of leukemia developed (Neumann) from an increased, or perhaps even a specific, irritation, the result of the simple reparative hyperplasia of the blood-making organs (particularly the bone-marrow). In support of this view cases are described in which a severe anemia became transformed into acute leukemia. Strauss especially advocates this view and regards the relative lymphocytosis in pernicious anemia (noted in this volume) as a further indication that this disease may be a preceding stage of lymphatic leukemia. Still another support for this theory is found in the assumption

[1] No positive decision can be arrived at as to the kind of leukemia in the cases of Sänger and Cameron, in which the children of mothers affected with chronic leukemia were born healthy, yet we are assured, at least, that there was no transference of the disease from mother to child. No special conclusion can be drawn from the death of the child immediately subsequent to nursing from its leukemic mother in Cameron's case.

of a common origin—that is, a common development stage for the lymphocytes and the red blood-corpuscles. This common origin is, however, not proved and is likewise improbable. The elucidation of this difficult problem requires much more thorough investigation. Every new work opens up new points of view (Brandenburg, Nägeli, Loewy and Schur, Paviot), which show the defectiveness of our knowledge in regard to the round cells of the bone-marrow.

DIAGNOSIS.

From the numerous observations published in the last ten years, acute lymphatic leukemia is no rarer than the other varieties of leukemia. In fact, from recent studies, it is probable that not a few cases have been described as severe purpura, scorbutus, morbus Werlhofii and the like, which were really acute leukemia. This idea is supported by the frequent cases of purpura in which a more or less high grade of leukocytosis is found in the blood (Denys).

The most important factor in the diagnosis is the positive *evidence of the blood-alteration.* For, on the one hand, there are cases with hemorrhages from the skin and mucous membranes which are distinguishable only by the normal appearance of the blood, and, on the other, a series of cases in which after an aleukemic course (or, more accurately, cases which seem to be only severe anemia) a marked leukemic change suddenly occurred in the blood shortly before death, unannounced by any new clinical symptom (Körmöczi).

When typic symptoms are present in a marked degree, as, for instance, an immense splenic tumor, intense glandular swelling, advanced alterations in the mucous membrane of the gums or mouth, associated with a striking pallor and puffiness of the face, severe hemorrhages associated with irregular fever or none, it is easy from the clinical symptoms alone to exclude the similar diseases that may come into consideration (typhoid fever, scorbutus, trichinosis) and arrive at a proper diagnosis. Bradford and Shaw contend that after diagnosing their first case, all others were readily recognized.

If these symptoms are less in degree, it is impossible from them alone to make a diagnosis. There is only one sign on which the diagnosis can be based with certainty—namely, the appearance of the blood. A marked and progressive increase of lymphocytes (see table, p. 555) occurs only in lymphatic leukemia, though naturally in the chronic as well as in the acute form—which makes it impossible, from the blood-finding alone, to separate these two. It is true that for a time the large size of the cells in this lymphocytic increase was regarded as indicative

of acute leukemia and of acute exacerbations of chronic leukemia; but after acute leukemias with an exclusive increase of the small variety were recognized, and chronic cases with an increase of the large cells, this differentiation lost its decisive character (A. Fraenkel). Among the clinical differences we find that the general aspect, the slight swelling of the spleen and the glands, the rapid course with hemorrhage and ulceration, make the differentiation from chronic leukemia sufficiently marked, yet such a differentiation from an acute exacerbation of chronic leukemia is frequently impossible, and then can be made only by the anamnesis.

In relation to acute pseudoleukemia, from which acute lymphatic leukemia must be differentiated, nothing at this time can be stated with certainty. The few descriptions of this so-called disease at hand are too inaccurate and consider too little the principal factor—namely, the blood-examination. This applies even to the 2 cases described by Ebstein in his fundamental work. It is not at all improbable that a number of these cases should be reckoned with acute lymphatic leukemia. In Coleman's case 11,200 leukocytes were counted, among which 40 per cent. were lymphocytes. The histologic finding in the widespread large lymphomata was striking by its lack of mitotic figures.

The relation of chloroma to this disease will be studied in a subsequent section.

By the aid of the blood-examination alone it is possible to exclude all other similar diseases.

The diseases coming into consideration are, first, those which run a similar course with a status typhosus. Among these typhoid fever itself stands out preëminent. This may be confused not only clinically, on account of its general symptoms and the occurrence of decubital ulcers on the skin and in the digestive tract, but even on the post-mortem table. The anatomic differentiation, apart from the bacterial finding, between lymphatic leukemic and typhoid ulcers, especially in the intestine, is, in fact, not rarely impossible.

Further, diseases falling under the head of erythema multiforme and toxicum present to a certain extent similar appearances. This is true especially of those manifesting hemorrhages from the skin and mucous membranes, as the ordinary purpura rheumatica, morbus maculosus Werlhofii, and septic erythema. Moreover, we must include erythematous and hemorrhagic affections associated with ulceration and necrosis of the mouth, as well as the benign erythema multiforme bullosum (which is readily distinguished by its mild course) and scorbutus. Especially interesting in this regard is the previously mentioned case

of acute leukemia in a seventeen-year-old patient who never, or at most only rarely, ate fresh vegetables, a deficiency always named among the primary causes of scorbutus. Apart from the blood-finding, the diagnosis may be made from the histologic examination, since in leukemia the ulcers arise through the breaking down of the characteristic lymphadenoid tumors, although more or less marked accumulations of lymphocytes may be found in the neighborhood of hemorrhages produced by the hemorrhagic diathesis.

From the number of similarities it may be conjectured that many of the obscure hemorrhagic cases described as morbus maculosus, scorbutus, etc., were in reality acute lymphatic leukemia, especially since, with comparatively little attention to the blood-examination, an increase in leukocytes is mentioned in more than one of them (Denys, Zimmermann). We are confirmed in this view by the cases which at first run their course under the picture of a severe anemia, and only later, in fact a few days before death, show a rapidly occurring leukemic change in the blood (Litten, Körmöczi, Waldstein). Whether these cases are to be considered leukemia from the beginning, or whether the leukemic blood-finding represents only the symptom of a still obscure affection, can not at present be decided, on account of our defective knowledge of the nature of these processes. Nevertheless, these occurrences force us to insist all the more on the rule enjoined by Mosler, forty years ago, that in every obscure case of a suspected blood-disease *the blood should be carefully examined at short intervals.*

PROGNOSIS.

The prognosis of acute lymphatic leukemia seems to be absolutely unfavorable. So far there is no known case where the patient lived longer than a few weeks after the determination of the diagnosis. The duration of the disease may in extreme cases be only a few days, as is shown by the blood-finding in those in which the disease was preceded by a carefully investigated anemia. Still, on account of the insidiousness of the beginning, which may be practically without symptoms or may present the picture of another disease, it is often impossible to give an absolute opinion as to the duration. It is not sufficient to know the condition of the organs usually affected (glands, spleen, visible mucous membranes and tonsils) in order to say when, during the symptomless period, the beginning occurred, but an exact knowledge of the microscopy of the blood is necessary.

It is impossible to make definite statements as to the length of time

a leukemia may be looked upon as acute. A duration of four to six weeks may be taken as an average, yet there are many deviations. Ebstein considers nine weeks as the longest period, although undoubted cases are known of several months' duration. The general picture of the disease will prove a much better criterion than any determined time, which can be stated only empirically and may be overthrown by any new observation.

A marked remission (with general recuperation and return of the blood to almost the normal, giving the impression of a possible cure) has been observed in the course of the disease in a very few cases. Moreover, after a short time the old symptoms recurred, to progress more rapidly than during the first attack, and always led to a fatal termination.

Death has frequently been hastened by intercurrent septic infection, for which the leukemia acts as a good soil; again, it has been brought about several times by a complicating pneumonia.

In an uncomplicated case death occurs either as the result of symptoms (hemorrhages, for example) belonging to the disease, or of gradual exhaustion terminating in collapse.

TREATMENT.

Thus far we have never succeeded in calling a halt to the pernicious course of the disease. The means employed with a certain amount of benefit in chronic lymphatic leukemia and its near ally, pseudoleukemia, are completely useless, either internally or subcutaneously—we mean, particularly, arsenic and the organotherapeutic measures (bone-marrow, thyroid gland and similar preparations). The remarkable but rapidly transitory influence on the blood of the injection of defibrinated blood, organic extracts and chemic substances (like spermine zimtsäure) will be taken up in the discussion of chronic leukemia, in which they are almost exclusively employed.

Further investigation of the etiology leaves therapeutic advance to be expected. Yet, for the present, we can only hope to alleviate the sufferings of the patient without being able to check the disease. The mouth symptoms, the necroses on the skin and mucous membranes, require local treatment, and are frequently improved by these means (Kübler). Every injury that might lead to the readily occurring and pernicious decubitus must be especially avoided. Yet, on the whole, as Gilbert and Weil have appropriately said, the physician's power stops with the making of the diagnosis, signifying, as it does, the most unfavorable prognosis. Therapeutically, we are powerless.

CHLOROMA.

This disease, described since the beginning of the nineteenth century under the names chloroma (King), chlorolymphoma (Waldstein), and green cancer (cancer vert d'Aran), bears an extraordinarily close resemblance to acute lymphatic leukemia. Its peculiar nature was first explained by the recent work of v. Recklinghausen, Dock, Paviot, and Lang.

The chief clinical symptoms are exophthalmos produced by a retrobulbar lymphoma development, deafness, and swelling of the occipital and temporal regions. Following these, sooner or later, a rapid leukemia develops, manifesting the same symptoms which we have learned to recognize in acute leukemia, with the same invariably fatal termination.

The disease obtains its name from the green color of the tumors, a color which is occasionally seen in otherwise typic cases of acute leukemia (especially in the bone-marrow).

The disease is much rarer than acute leukemia. [Dock, in his paper published in 1893, reported 1 case and collected 16 others from the literature. In a second paper, Dock and Warthin[1] have collected the cases from 1893 to 1904. Including their own, they find 22 cases, and they refer to a few unpublished instances or cases simply alluded to in discussions.—ED.] It shows a predilection for childhood and the male sex even more markedly than acute leukemia. [Of the 22 cases in Dock's later series, 3 were females and 19 males, while in his two series there were 9 females and 29 males. The average age was 18.8 years in the later series, which is 3½ years older than in the former series. In part, this was due to the fact that 4 of the cases occurred in persons between 38 and 52 years. Fifteen of the cases were less than 25 years old, 12 less than 16, and 1 only 10 months old. Heyden,[2] in his monograph, refers to 37 cases, in 31 of which the age of the patient is stated. He tabulates them as follows:

0 to 5 years	4 cases.
6 " 10 "	8 "
11 " 15 "	6 "
16 " 20 "	5 "
21 " 25 "	4 "
28–44–51–52 years	each 1 case.—ED.]

An immediate cause for the disease has not been demonstrated, provided the isolated mention of an ocular trauma (Hillier) is not considered as such. It is possible that the "lymphatic constitution" in children creates a predisposition toward the disease.

[1] *Trans. Assoc. of Amer. Phys.*, vol. xix., 1904.

[2] *Das Chlorom*, Wiesbaden, 1904.

The first striking symptom is usually the *exophthalmos*, accompanied by intense pain in the orbital cavity. Soon after, disturbances of vision and difficulty of movement of the bulbus oculi appear. A short time later a hard, smooth swelling develops, which is palpable through the eyelids, and, in a case with recurrence after extirpation of the bulb, was visible as a grayish-yellow tumor (Hillier).

[Heyden[1] states that in 14 of his cases exophthalmos was the first symptom in the majority of them. This was accompanied by deafness with or without otorrhea. In 6 of the cases the first manifestation was some pallor, and in 2 swelling of the region of the temples. In 1 case petechiæ were first observed. A few authors have referred to primary swelling of the glands. In 18 cases of Dock's later series, in which the clinical histories are given, early weakness was noted in 9, pallor or anemia in 11, exophthalmos in 11, swelling and eversion of the lids in 1, deafness in 10, swelling of the temporal region in 9, swelling of the face in 3 more, enlarged lymph glands in 8, emaciation in 6, rapid pulse in 6. Pain was often a prominent symptom; it was most frequently felt in the head, eyes, teeth or ears, or in the hips or legs. Hemorrhages into the skin and mucous membranes occurred in 8 cases; blindness in 4; enlargement of the liver in 3, of the spleen in 7. —Ed.]

Retinal hemorrhages and whitish infiltrations are found in the posterior eye-ground.

Simultaneously with the orbital swelling a hard symmetric *swelling of the temporal regions* develops, accompanied by difficulty in hearing, even to complete deafness, loss of sensation, and sometimes slight disturbances of equilibrium (staggering gait). [In Dock's second series deafness was as conspicuous as in the former series. He refers to the case of Koerner, and to the fact that this observer found evidence of ear symptoms in 10 of 20 cases of chloroma.—Ed.] During this time the normal skin color gradually yields to a striking wax-like pallor, the patient emaciates and weakens. The lymph glands and spleen enlarge. Occasionally tenderness on pressure develops over the sternum. The blood is often *lymphemic* from the first examination or becomes so suddenly a short time before death (Waldstein, Paviot, and Fayolle), although in the beginning it may show no change or only a marked anemia. [The blood-picture in chloroma may be very varied. In 13 out of the later series of Dock, the conditions were quite characteristic of leukemia, though in 1 of these cases the leukocytes were not increased in number. In the other cases of the series, either no blood-

[1] *Das Chlorom*, Wiesbaden, 1904.

examination was made or the data were indefinite. In 10 of the cases the blood resembled that of acute leukemia, according to those who reported the cases. Dock and Warthin, in their conclusions, state that the blood-picture may be very varied, and if this be used as the basis of classification, it is possible to designate different varieties of chloroma. They believe that the white cells of the blood are derived from a hyperplasia of the parent cells of the leukocytes, primarily in the marrow, the periosteum being involved secondarily. This hyperplasia may result in the formation of cells of different character, either large lymphocytes or neutrophile or eosinophile myelocytes. At different stages atypic forms may be observed. It is uncertain whether a small lymphocyte type exists. When the hyperplasia of the parent cells is at such a stage that the new cells do not get into the blood, there is an aleukemic chloroma. The involvement of the bone-marrow cells by crowding out erythroblastic elements leads to severe anemia, which is one of the chief features of the disease. This anemia is due to deficient hematopoiesis and not excessive hemolysis.—Ed.] Moreover, as in acute leukemia, the increase is especially of the large lymphocytes. Hemorrhages from the skin and mucous membranes (sponginess of the gums, which bleed easily) make the picture more and more like acute leukemia.

The previously mentioned swelling of the orbits and the temporal regions is not absolutely necessary to the disease picture; as a matter of fact, it is wanting in isolated cases; and the disease then runs its course to death under the picture of a marked anemia with rapid exhaustion. In 1 of these cases the only symptom of chloroma perceptible during life was the green discoloration of the urine (Waldstein).

The pathologico-anatomic changes are, in general, those of acute leukemia, to which are added a number peculiar to chloroma.

The most striking peculiarity is the *green color* of the tumors. Highly characteristic is the lymphoma formation on the face and cranium, seen clinically. The osseous system is especially affected. The bone-marrow suffers often, even though not constantly, so far as we know, being replaced by a greenish, or frequently a pure pea-green, mass of somewhat increased consistence (see the picture in Dressler's work). [In 7 of Dock's later series, changes in the bone-marrow were discovered. It must be remembered that examinations of the bone-marrow can not be made with absolute thoroughness, and in a number of the cases no examinations at all were made.—Ed.] More widespread, yet less marked, are the changes in the bones themselves. Lymphogenous green tumors are deposited in all the facial and cranial bones, either under or in the periosteum or dura mater respectively.

The sutures are forced apart even when the bones themselves are but little affected, and the neoplasm grows through all the openings, filling up the orbital and tympanic cavities.

Similar chloromatous masses are found within and on the outside of the spinal column, the ribs, the sternum, the pelvic and shoulder girdles, and sometimes even the long bones, so that, in spite of the small number of observations, almost every bone has been mentioned once or oftener. The marrow of the tubular bones is similar to that of the others—namely, pea-green, and may contain large quantities of Charcot-Leyden crystals, which are wanting in lymphatic leukemia. Their presence in conjunction with the guaiac reaction (see p. 580) supports the view that cellular elements other than lymphocytes must participate in the building up of the chloromatous masses.

The lymphatic organs are almost as markedly affected as the bone-marrow. A green swelling of the lymph glands, especially of the head and neck, arises, and we find tumors on the tongue, palate, and pharynx. [The lymphatic glands were frequently involved in Dock's series, but in 1 case it was expressly stated that the lymphatic glands were without pathologic changes. Heyden,[1] referring to the matter of glandular enlargement, states that apparently all cases have been attended with swelling of the lymphatic glands. Those of the extremities and of the bronchial region are most frequently involved; less frequently the abdominal and pelvic glands.—ED.] The salivary glands (parotid, submaxillary) are infiltrated with lymphatic tissue, the thymus and pancreas are partially replaced by green masses. Peyer's patches and the lymph follicles of the intestine are grayish green, often swollen, and sometimes ulcerated and riddled with hemorrhages. The spleen is enlarged on account of an increase of lymph tissue. The kidneys and liver contain green lymphomata, some superficial, others well within the parenchyma. Moreover, analogous to the infiltrations in acute leukemia, the round-celled greenish accumulations accompany only the branches of the portal vein, while the hepatic vein remains free (Paviot). Similar masses are found in the lungs and pleuræ. The nervous system alone is exempt. The symptoms proceeding from it, like blindness, deafness, and paralysis, are usually referable to compression by externally situated chloromatous masses or to disturbances of the nerve endings.

The histologic structure is that of a lymphoma, and consists partly of small, partly of large, mononuclear round cells deposited in a delicate reticulum. The green coloring-matter appears in the form of small

[1] *Das Chlorom*, Wiesbaden, 1904.

strongly refractive granules, situated in the cells of the tumor masses. The reaction of these pigment granules would seem to indicate a fatty composition. They are green from the beginning, or become so after short exposure to the air. Later they take on a dirty color and may so remain for several days, or disappear suddenly when exposed to the air, though they may be made visible again by treating with a solution of ammonia (Paviot and Hugounenq). They are decolorized by alcohol to a dirty gray. The pigment is soluble in absolute alcohol and ether and is stained dark by osmic acid (1 per cent.). It fails to respond to the iron reactions (Höring). It stains old *tincture of guaiac* at once blue; becomes blue itself and (in sections) retains this color for ten minutes. Following this the tissue is first decolorized, and then the solution (tincture of guaiac) changes to a dirty yellowish green. The preserving fluid undergoes the same reaction. On immersion in boiling water the tumor loses its oxidizing properties. After contact with paraphenylendiamin for twenty to thirty minutes, the chloroma is stained a dark violet (Paviot and his co-workers). This reaction is not given by chloroma alone, but is the common property of many rapidly growing tumors. Moreover, the guaiac reaction occurs in connection with the richly cellular bone-marrow of pernicious anemia (Naegeli), while it is wanting in organs filled with lymphocytes (Brandenburg). [Referring to the color of chloroma, Dock concludes that the cause of the green color is unknown, though it probably belongs to the group known as parenchymatous colors. It is possible that processes morphologically like chloroma may lack the characteristic color. Such cases should be classed with non-chloromatous leukemias.—Ed.]

In the early cases the diagnosis of chloroma was usually made only after death, less on account of the possibility of confusion with other diseases than on account of the uncommon clinical picture, which made the affection appear as something new—unknown. Still, the likewise very rare cases of symmetric disease of the salivary and lacrimal glands, which, from a pathologico-anatomic standpoint, also belong to the lymphatic hyperplasias, show a great similarity to chloroma. They are differentiated by their longer duration and the relative mildness of their course. We will discuss them more in detail in dealing with chronic lymphatic leukemia and pseudoleukemia.

The prognosis of chloroma is always unfavorable. Death follows in from several weeks to several months.

The therapy is quite as futile as in acute leukemia. Operative interference has likewise been without result (Hillier).

CHRONIC LYMPHATIC LEUKEMIA.

UNDER the definition of chronic lymphatic leukemia are included those cases which run their course in from several months to years with a hyperplasia of the lymphatic apparatus and an increase of the lymphocytes in the blood. This type was differentiated first by Virchow. Its boundaries were sharply defined by Neumann and Ehrlich, corresponding to the advance in our knowledge. In spite of this early histogenetic definition, we frequently find cases in which the kind of leukemia was diagnosed by clinical symptoms other than the lymphocytosis; for instance, the presence or absence of glandular or splenic enlargement. Further, we meet a large number of cases which, according to the general clinical picture, would be included under the head of pseudoleukemia or malignant lymphoma (that is, an affection simulating lymphatic leukemia, with or without some alteration in the proportion of whites to reds), but in which a lymphatic alteration of the blood is recognized by modern staining methods.

If we follow the conclusions of the above-mentioned investigators, lymphatic leukemia should be excluded from either of the classes mentioned; from the former, on account of the general clinical symptoms—*e. g.*, the lymph-gland swelling; and from the latter, on account of the blood-picture.

In other words, our guiding criterion must be the principle laid down in the consideration of acute lymphatic leukemia—namely, that the diagnosis of a leukemia and its variety can be based only on the appearance of the typic blood-change, and that the other clinical symptoms are of secondary importance.

This brings us to the consideration of the question which was discussed briefly in the introduction, and which must first be thoroughly understood, so far as our knowledge goes, before we take up the description of chronic lymphatic leukemia.

From the beginning, the blood-finding has been considered the only absolutely certain characteristic in the diagnosis of leukemia. All other symptoms are to be regarded as inadequate, since cases are known which

simulate leukemia in every way except in the marked increase in white blood-corpuscles; in fact, these cases are called, on this account, pseudoleukemia. True, the cases of pseudoleukemia corresponding to the type of malignant lymphoma are frequently very different from the average lymphatic leukemia. Still, we have all sorts of transitions—from this type, which gives more the impression of a local enlargement of lymph glands, to the types exactly resembling lymphatic leukemia.

While in extreme cases the clinical differentiation is easy, in others the boundary is ill defined, since, as we have known for some time, a moderate alteration of the blood is not rare even in pseudoleukemia. In fact, a number of investigators, taking their cue from the experience of recent years, consider the leukocytic increase neither as characteristic of leukemia nor contrary to the assumption of pseudoleukemia. Even lymphocytoses of high degree are sometimes ignored in the decision.

This uncertainty forces us to the conclusion that it is impossible to separate accurately histogenetic lymphatic leukemia from pseudoleukemia; and it becomes necessary, therefore, to include these two affections in one group as closely related diseases.

In this group very different clinical pictures are associated with the common bond of lymph-gland enlargement and lymphocytosis. Among these, two fundamental types may be differentiated: one including the cases with a marked degree of lymphocytosis—*genuine lymphatic leukemia;* the other including those with no marked deviation of the proportion of W. : R.—*lymphatic pseudoleukemia.*[1]

A sharp line can not be drawn between these two groups. Moreover, if we consider the blood-finding the most important clinical symptom, the diagnosis of genuine leukemia must be based on the numeric proportion of W. : R., which rather limits its value. In general the boundary line lies between (W. : R.) 1 : 100 and 1 : 200. Smaller quotients are to be reckoned to pseudoleukemia, larger ones to genuine leukemia.

The existence of lymphocytosis in these cases allows them to be differentiated from several other affections which are clinically very similar, but in which this symptom is wanting. In the absence of this lymphocytosis we must consider another etiology for the enlargement of the glands as probable; in fact, so far this probability has been veri-

[1] The term lymphatic pseudoleukemia is not used to imply a contrast with any other terminology (*e. g.*, myelogenous pseudoleukemia); for there is no other form of the disease than the one associated with enlargement of the lymph glands, and lymphemia stands unique. The designation "lymphatic," therefore, is to be taken only as a histogenetically explanatory adjective.

fied in every case which came to autopsy. [Ewing[1] states that "in the less-marked stages of lymphocythemia, especially of the acute form, the number and proportion of lymphocytes may be far from characteristic of leukemia. When there are less than 150,000 leukocytes and less than 90 per cent. of lymphocytes the condition of the blood does not differ from that seen in some forms of inflammatory leukocytosis, or of lymphocytosis in the secondary anemia of children, or of the obscure condition called 'v. Jaksch's anemia.' In inflammatory lymphocytosis, however, there are always a fair proportion of polynuclear leukocytes, which are very scanty in lymphemia, and the lymphocytosis is usually transient."—ED.]

In regard to the cases without lymphocytosis, there are two possibilities:

1. That we have to do with a stage of lymphemia in which the alteration of the blood has not yet appeared, on account of the short duration of the process; or with a terminal stage, complicated by septic infection from which a previously existing lymphocytosis has disappeared.

2. That we have to do with another disease—for instance, peculiar forms of tuberculosis, which we will describe more thoroughly when speaking of the differential diagnosis; or the unique affection which Kundrat has differentiated from the large group of lymphatic tumors under the name lymphosarcomatosis.

We therefore consider ourselves justified in including under one head all cases manifesting a lymphocytosis. On account of the marked clinical differences in these cases, it is not improbable that quite heterogeneous processes—that is, processes etiologically different—have been artificially combined. Still, we have no means of making a better classification. The simple division according to localization, previously in vogue, is not sufficiently comprehensive and accurate, since we have to do with exactly the same pathologico-anatomic phenomena in the different places. [Ewing[2] refers to endothelioma of the lymph nodes as the anatomic basis of a case of lymphatic leukemia studied by him.—ED.] Perhaps the long-desired explanation may be brought forth by the further investigation of the nature and etiology of the disease.

[1] *Clin. Path. of the Blood*, 2d ed., p. 250.
[2] *Ibid.*, p. 239.

LYMPHATIC LEUKEMIA.

SYMPTOMS AND COURSE.

Onset.—The onset of chronic lymphatic leukemia is, in the majority of cases, gradual and insidious. The few observations relating to an acute beginning are by no means sufficiently clear to refute the objection that they represent acute exacerbations or the occurrence of an acute intercurrent disease in the course of a previously existing, though latent, chronic leukemia. In acute leukemia the determination of the beginning is frequently difficult on account of ignorance of the condition before the primary observations, and is possible in only a few not very typic cases of especially rapid course; but in chronic leukemia we have almost no criterion by which to draw a sharp line between health and the onset of the disease.

The enlargement of the lymph glands, observed early in many cases, makes, to a certain extent, a time boundary. For when a long-continued anemia associated with widespread enlargement of the lymph glands calls attention to a disease of the blood-making organs, we usually find such a marked alteration of the blood that a long existence of the affection can be concluded. Still, enlargement of the lymph glands is not rarely wanting till toward the end of life, and then only an accidental examination of the blood discovers the lymphemic condition.

Since, therefore, no certain time can, as a rule, be set for the beginning of the disease, we must consider that the alterations occur slowly and imperceptibly till the disease is so far advanced as to produce subjective complaints and objective symptoms.

As has been mentioned, the most frequent symptom to call attention to the disease is the enlargement of the **lymph glands.** This enlargement may exist with otherwise perfect health for a long time, even years. In this case it is usually slight, but it may at any time rapidly increase to extraordinary dimensions. The enlargement may be regularly distributed over the different regions of the body; although, much more frequently, it is more or less limited to one or several groups. Immense lymphomata are observed most commonly on the neck. They are usually associated with rather large ones in the axilla and smaller ones in the groin—in other words, there is, as a rule, a decrease in size from above downward. Still, not rarely the largest glands are found in the axillæ and occasionally in the groin and thigh. It sometimes happens that an enlargement is scarcely perceptible externally, but,

post mortem, immense masses are found in the chest, abdomen, and pelvis (Ehrlich and Wassermann). In rare cases we find no enlargement worthy of mention.

The glandular masses consist of single lymphomata well separated from one another, varying from a very small size to that of an egg or an apple. Adhesions between the glands are extremely rare, and are practically always to be referred to malignant degeneration or complicating periadenitis, which is not a feature in the actual picture of leukemia. The shape of the individual gland is unexceptionally ellipsoidal, with equal or unequal short axes, or egg-form. It is sometimes flattened out by the lateral pressure of other glands or structures in the neighborhood (skin, underlying soft tissues). The consistence in the genuine leukemic cases, the blood of which shows a marked derangement of the proportion of whites to reds, is almost always soft and elastic, usually simulating that of the normal testicle, and is only rarely hard, even to bony hardness, as in pseudoleukemia, the blood of which shows only a relative increase of lymphocytes.

In addition to the disfiguration of and loss of motion in the part, the symptoms directly arising from the enlargement of the glands, though of infrequent occurrence, consist of pain, which is usually slight and but rarely of marked intensity, and of the more important results of pressure on the vital organs. Among the latter, compression of the trachea and of the vascular trunks most frequently gives rise to disagreeable symptoms.

The glandular tumors continue to increase in size till the termination of life, provided an intercurrent disease (erysipelas, septic infection, cholera) does not cause them to disappear, as in acute leukemia.

Among the other blood-making organs, the **spleen** alone manifests physical signs of disease. Its enlargement is almost a constant accompaniment of chronic lymphatic leukemia. Very large spleens are sometimes seen, though, as a rule, the enlargement is not so great as in myeloid leukemia, in which the whole left side of the abdomen is often taken up by the tumor, which extends to the right beyond the umbilicus and downward into the small pelvis. The splenic tumor of lymphatic leukemia is movable within moderate limits. In size it usually extends several fingers' breadth beyond the border of the ribs, and when it reaches the umbilicus it must be considered very large. The enlargement takes place regularly in all directions, so that even when considerably enlarged it retains its typic form. The size of the spleen is, in general, dependent on the duration of the disease, since it usually grows slowly and continuously till death. Nevertheless, since the rapidity of

the enlargement varies in different cases, we find in some, after a short duration, very large tumors; in others, after the same length of time, even when the other symptoms are marked, only moderate-sized ones. The very large and hard spleens seem, as a rule, to belong to the cases manifesting a small lymphocytosis in the blood.

That an actual enlargement of the spleen is not absolutely necessary to lymphatic leukemia was demonstrated in the first case described by Virchow, in which the organ presented no macroscopic abnormality beyond a certain hardness. The same condition has been reported in a number of recent observations.

An exception to the rule that the growth of the leukemic spleen continues till the end of life is seen in the cases (previously mentioned) of bacterial infection, as well as in those in which an acute exacerbation of the leukemic process takes place *sub finem vitæ*. General septic infection and localized suppuration are the most frequent factors in dissipating the lymphemia, so that the enlargement of the lymph glands and spleen diminishes and the blood not rarely loses its lymphemic character, and even goes over into a condition of polynuclear leukocytosis. Still, this influence of a septic infection is by no means the rule. Leukemic patients may pass through these complications without any change in the lymphemic symptoms (Hirschlaff).

A decrease in the splenic tumor has also been observed following long-persistent diarrheas, which sometimes arise in connection with the medication (iodoform) or other therapeutic measures. This decrease can only rarely be regarded as an improvement of the general leukemic condition. Moreover, in the cases in which an improvement of the general condition is associated with a diminution of the splenic tumor, the numeric proportion of whites to reds usually changes but little or may, indeed, become more marked. Several rare cases of apparent recovery will be discussed later.

The alteration of the **bone-marrow**, to which Neumann first called attention as a constant finding, is usually marked, yet in contrast to the similar condition in myelogenous leukemia and to the specific tumor-like lymphadenoid disease of the marrow in the affection known as multiple myelomata (Rusticki) or lymphadenia ossium (Nothnagel) it only rarely gives rise to clinical symptoms. Intense pain in the bones is usually the result of secondary infection of the periosteum and abscess formation. Litten especially has drawn attention to the fact that the tenderness of the bones, which is considered typic, may be wanting in the most advanced cases of disease of the marrow. In lymphatic leukemia it is practically never present.

The symptoms produced by the development of lymphomata in organs other than the blood-making ones will be discussed later. We wish to deal first with the characteristic symptom of lymphatic leukemia—namely, the *blood-picture.*

Alterations in the Blood.—The principal symptom manifested by the blood is the *increase in lymphocytes.*

In the general increase of leukocytes observed the lymphocytes participate to a marked degree, both relatively and absolutely. The relative increase in lymphocytes is especially striking, and, since it is easier to determine than the absolute number, it is particularly useful in the diagnosis. It is not rare with a proportion of whites to reds of only 1 : 100 (which requires only about 20,000 white blood-corpuscles, on account of the almost constant oligocythemia) to find 90 to 96 per cent. of lymphocytes. With a greater proportion of whites the relative lymphocytosis may increase even to 99 per cent., producing an almost complete absence of all the other varieties of leukocytes.

The lymphocytes of chronic lymphatic leukemia belong, in by far the great majority of cases, almost exclusively to the small variety. They are the same size as, or smaller than, the red blood-corpuscles, and show a small amount of protoplasm and a round, usually feebly staining, sharply circumscribed nucleus with a round, clear vacuole (nucleolus). The protoplasm is basophilic to methylene blue and is often filamentous at the margin. Medium-sized and large forms, which are the common ones in acute leukemia, may be found, though usually rare; there are, however, very chronic leukemias which show only the large variety.

A considerable number of the lymphocytes circulating in the blood (sometimes more than one-tenth of the entire number) manifest signs of degeneration, as has been shown especially by Gumprecht. The destruction of these cells begins in the nucleus, and is manifested either by a more intense staining and subsequent breaking up into intensely stained fragments (karyorrhexis), or by a swelling accompanied by a loss of staining power and the formation of peculiarly large dentate forms (karyolysis), often resembling an oak leaf (Askanazy). The protoplasm of the cell degenerates later. To what extent these alterations of the lymphocytes are to be regarded as true retrograde metamorphoses must be left for future investigation. On account of the absence of these degeneration forms in fresh unstained preparations, Askanazy believes that they represent abnormalities artificially produced in the readily compressed lymphocytes, especially since they are much more frequent

in the thin crushed portions of the smear than in the usually thicker marginal portions.

The other varieties of leukocytes participate in the increase only exceptionally and then in a slight degree. In fact, their number is usually quite considerably lessened in comparison with the normal. This diminution affects especially the neutrophile polynuclear cells, which constitute normally the greatest number. Their relative number is decreased by the increase of lymphocytes from the normal figures of about 70 per cent. to 10 per cent. or even less, and, not rarely, to even 2 or, indeed, 1 per cent.

Eosinophile cells are usually found; mast cells are seen in only extremely small numbers. Myelocytes are wanting in almost all cases.

The number of red blood-corpuscles frequently remains normal for a long time, or is only insignificantly decreased (to 4,500,000 or 4,000,000). With the appearance of cachexia their number gradually decreases, though it seldom sinks much below 2,000,000. Nucleated red blood-corpuscles are rare, and other alterations are only exceptionally described.

The percentage of hemoglobin about corresponds to the number of red blood-corpuscles.

Some increase of lymphocytes is always found on the first examination, after other clinical symptoms (especially the enlargement of the lymph glands and spleen) have given cause for the investigation of the blood. Moreover, when the first examination is made a longer time before the fatal termination we find, in the course of further observation, a gradually progressive increase, with rare slight remissions, in the whole number of leukocytes and the relative number of lymphocytes, so that at the time of death the number of lymphocytes is usually higher than at any preceding period.

Spontaneous diminution and even complete disappearance of the lymphocytosis has been observed several times. Sometimes, in its place, a polynuclear leukocytosis is seen. This alteration of the blood-finding is usually the result of some bacterial complication. Very exceptionally, in these cases, recovery of both the complication and the original disease has been reported (Delens, Mager).

The other symptoms of chronic lymphatic leukemia are dependent on the *development of lymphatic tissue* in the organs. They are the result of the new growth, on the one hand, and of the mechanic limitation of the functionating parenchyma, on the other. The appar-

ent toxic effect of the rapid destruction of tissue seen in the prostration, the fever and the altered metabolism of acute leukemia is only suggested, when the chronic form takes on, *sub finem vitæ*, a course simulating the acute. Every sign of deeper organic change is wanting; even the pallor of the skin, in other forms of leukemia a most conspicuous symptom, has never been observed.

Highly interesting **alterations of the skin** occur in rare cases. A very mild condition is an intense itching of the entire skin, which is usually dry and withered, this condition being frequently associated with an eruption of urticaria papulosa and vesiculosa. Preceded by the sensation of burning and itching, hard yellowish-white wheals with a centrally situated vesicle suddenly appear. These are distributed irregularly over the whole body, though especially on the arms and legs, as in other lymphomatous affections (malaria with splenic tumor, pseudoleukemic, like lymph-gland tuberculosis). At the site of the wheals which have been scratched, small granulation tumors sometimes form, to disappear again after a short time.

The occurrence of lymphomata in the skin, either as small tubercles, varying in size up to that of a bean, distributed over the whole body, or as larger nodules showing a special predilection for the face, is more striking and has been more frequently described. Projecting, sometimes even overhanging, tumors are seen on the eyebrows, eyelids, cheeks, nose, lips, and chin; and, on account of their shape and reddish-brown to bluish-red color, give a peculiarly disgusting appearance to the face, already disfigured by large lymphomata about the ear and chin. Smaller tumors are found, more rarely, on the arms (Nékám), especially the elbows, the backs of the hands and fingers, and on the legs (knee). The tumors grow slowly but continually, and show little inclination toward breaking down (Kreibich, Pinkus).

A third variety of skin affection is known under the name *lymphodermia perniciosa* (Erythrodermie mycosique of the French). It begins as a peculiar, intensely itchy sensation, accompanied usually by universal redness and swelling of the skin, to which, after a longer or shorter time, the general symptoms of lymphatic leukemia are added. After this has existed for years, tumors like those previously described often develop in the skin, especially of the face, giving it a leonine appearance (Kaposi).

Mycosis fungoides is not a characteristic of lymphatic leukemia, although its French name, lymphadénie cutanée, was given by Ranvier on the supposition that it was a sort of pseudoleukemia of the skin. This supposition proved to be unwarranted.

[Nékám[1] discusses leukemia of the skin and distinguishes 2 groups of cases; the first being cases in which the circulation of the skin is disturbed; and, second, the cases of true leukemic disease of the skin, causing the formation of nodular masses. In the latter group, a diagnosis must be made from cases of tumors of the skin with leukocytosis. The lymphodermia perniciosa of Kaposi he regards as a mycosis and distinguishable from true leukemia.

Of the 4 cases of skin lesions in association with leukemia reported by the author, 1 he regards as a true leukemia of the skin. It was found in a woman aged forty-one, who suffered from an eruption of soft nodules in the forearm. These became reddened and subsequently quite dark red from rubbing, and there was sometimes marked itching. Later, other parts of the body were involved. In addition there was diffuse brownish pigmentation of the skin and punctiform hemorrhages appeared. The lymphatic glands were enlarged and the bones became painful on percussion. The number of white corpuscles was as 1 : 3.5 of the red; and of the white 96 per cent. were lymphocytes.

Oertel,[2] in discussing the same subject, states that there are 3 kinds of cases. In the first there are small nodules, of pale or reddish color, scattered over the body; in the second, a few solitary, lobulated nodules; and in the third, more diffuse, moist and eczematous lesions or ulcerating tumor-like elevations. He reports 1 case in a woman of forty, who had been ill for two years: The spleen was considerably enlarged, but this had been regarded as malarial. Some time before death, nodules appeared in the skin of the chest and arms, and then elsewhere. Examination of the blood showed enormous leukocytosis with myelocytes and eosinophiles. The patient passed out of observation, but after death an autopsy was obtained and sections of the skin showed a dense small-cell infiltration, most of the cells being lymphocytes in the lower part of the cutis. No myelocytes could be identified and only an occasional plasma cell appeared.

Pinkus[3] also refers to this subject and reports 3 cases, all in persons of advanced years and having the symptoms and blood-conditions of lymphatic leukemia. The author points out that the same microscopic features may occur in pseudoleukemia as are found in lymphatic leukemia, and that there may be in the blood a gradual transition from one to the other disease. He distinguishes three classes of tumors of the skin associated with lymphemia: (1) Lymphatic tumors; (2) combination of sarcoma of the skin with lymphatic leukemia; and (3)

[1] *Monatshef. f. Prakt. Dermatol.*, 1899, II. [2] *Jour. of Exper. Med.*, 1899, vol. iv.
[3] *Archiv. f. Dermatol u. Syph.*, 1899, vol. l.

combinations of mycoses resembling mycoses fungoides and lymphatic leukemia.

In a case of acute leukemia under the editor's observation there was a general eruption of white and reddish nodules, which appeared in the skin a short time before death, and completely vanished during the last twenty-four hours of life. No histologic lesions could be discovered in the skin post mortem. The changes were attributed to circulatory conditions.—ED.]

Hemorrhages from the skin are not frequent. They occur principally during an acute exacerbation, such as is not rarely observed toward the end of life. Edema arises over all parts of the body, as a result of pressure of the lymphomata on the veins and the lymph vessels.

On account of the development of lymphomata in various *glands* of the face, a peculiar appearance is produced, very similar to that first described by Mikulicz under the name of symmetric-tumor formation of the lacrimal and salivary glands. To a certain extent, it simulates in its clinical aspect the picture which we described in Chloroma (Tietz, Kümmel).

The cases of this kind occurring in the course of leukemia seem to be extremely rare. True tumors arise in the lacrimal, parotid and submaxillary glands, but only in association with lymphomata that have arisen outside the glands in the connective tissue.

Combinations of sarcoma with lymphatic leukemia have been occasionally described. In some of the cases we have to do with spindle-cell sarcoma. The frequently described combinations of leukemia with round-cell sarcoma are open to the objection of v. Baumgarten, who demonstrated that the sarcoma-like pictures in pseudoleukemia are to be considered simply as pseudoleukemic formations. It would be difficult to prove that a round-cell tumor in a case of lymphatic leukemia was a round-cell sarcoma and not a leukemic deposit.

[Türk[1] records a case of acute leukemia with lymphosarcomatous lesions. The patient was a man of forty-one, who complained of pains in the limbs, followed by general weakness and further variable symptoms. Moderate enlargement of the spleen was found in the beginning, and later the spleen and liver increased greatly. The white corpuscles numbered 65,800, of which 55 per cent. were lymphocytes of unusual size and with a striking number of fat-droplets. Normoblasts were conspicuous. Later, the leukocytes increased still more and there

[1] *Mittheil. d. Gesellsch. f. innere Med. in Wien.* 11.9, p. 88, 1903.

were 70 per cent. of giant lymphocytes. The autopsy showed lymphosarcoma of the stomach, intestines, kidney, bladder, prostate, pelvic tissues, pancreas, heart, and pleura. The spleen, marrow, and the moderately enlarged lymphatic glands showed the histologic appearances seen in acute leukemia.

Strauss[1] records a case of sarcomatosis with lymphatic leukemia. The preparations from his case had been previously described by Virchow and published in the *Berlin. klin. Woch.*, 1898, No. 27. The leukocytes in this case numbered 32,000 to 65,000, of which 90 per cent. were mononuclear; the great majority of these being small lymphocytes.

Ewing[2] refers to a case of lymphatic leukemia in which he found endothelioma of the glands.—Ed.]

Albuminuria and casts in the urine as signs of *nephritis* are not common. Acute hemorrhagic nephritis occasionally occurs during the acute termination of a chronic leukemia.

The **liver** is frequently enlarged. Nevertheless, only the very marked enlargements give rise to subjective symptoms (intense pain from a complicating perihepatitis (Hall).

Diseases of the **vascular system** play an important though not as conspicuous a rôle as in acute leukemia. The brown degeneration of the heart, almost constantly present, gives rise to no prominent symptom, and the cardiac action itself presents no peculiarities apart from the rare cases of endocarditis, and these frequently are discovered only post mortem. Disease of the peripheral vessels is correspondingly frequent. Its results are noticeable in hemorrhages into all the organs, though the hemorrhages of chronic lymphatic leukemia are by no means so characteristic of the disease picture as those of acute lymphatic leukemia. They seem to be especially frequent in the terminal stages, when the disease has taken on a more rapid course and the blood shows the signs of a marked increase in lymphocytes. The distribution of the hemorrhages is differentiated in no way from that in acute leukemia. Apart from the ordinary locations (mentioned under Acute Leukemia), several special cases have been described; for example, hemorrhage from the iris and ciliary body into the anterior chamber (Sorger), fatal hemorrhage into the abdominal cavity following rupture of one of the internal organs (rupture of the suprarenal capsule has been reported several times (Fleischer and Pentzoldt).

Disease of the **nervous system** is infrequent in chronic leukemia. It consists partly in a lymphomatous development about and in the

[1] *Charité-Ann.*,[23] p. 434, 1898. [2] *Clin. Path. of the Blood.*

peripheral nerves, though more frequently in degeneration of the nerve fibers with or without preceding hemorrhage.

Paralysis of individual nerves and nerve groups are thus produced. The lesions occur in the spinal nerves (crural, sciatic), though more commonly in the upper part of the medulla oblongata and the cerebral nerves. Consequently, we find bulbar conditions with facial paralysis, anesthesia of the skin of the face, loss of taste, dysphagia, disturbances resembling Ménière's disease, difficulty of hearing even to deafness, and derangements of sight even to blindness.

The changes in the **ear** are often associated with the lesions of an old otitis, at the site of which the leukemia alterations occur in the shape of old or recent connective-tissue formation or organized remains of hemorrhages (Politzer, Gradenigo, Kümmel). Still, the disturbances of hearing appear to be produced more frequently by leukemic infiltrations and hemorrhages into a completely healthy ear (Schwabach). Occasionally they are brought about by central disease (degeneration in the medulla oblongata, Kast) or by disease of the auditory nerve itself.

The **ocular symptoms** are much more frequent, yet by no means so constant as in acute leukemia. Genuine lymphomata are extremely rare. They are observed most commonly on the conjunctiva and also occasionally on the iris. Hemorrhages, on the contrary, from the conjunctiva, iris, and ciliary body, as well as into the eyeball and its posterior wall, are frequent. The retinitis leukæmica, shown by the ophthalmoscope as white specks, infiltration of the vessels and hemorrhages, is especially characteristic.

As in the case of the ear, derangement of vision may be referable either to alterations in the eye itself or to lesions in the optic-nerve degeneration following lymphomatous infiltration or hemorrhage or in the more distant nervous apparatus (compression of the sympathetic (Chvostek).

In the course of the disease, weakness and emaciation set in, though they reach a high grade only in very protracted cases, and usually are not marked, even during complications at the termination of the disease. The **metabolism** shows no abnormality other than would be produced by the existing anemia. In acute exacerbations the tissue destruction (as judged from its products) approaches that seen in acute leukemia.

The occurrence of the so-called *Bence-Jones' body* in the urine has been reported in 1 case by Askanazy. This is an albumose which stands in close relation to the lymphadenoid alteration of the bone-marrow.

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It is precipitated by warming the urine and is dissolved by further heating. The precipitation begins at about 50° C. and is most marked at about 60° C. While cooling (after overheating) the precipitate again appears. The precipitate produced by acids or by a mixture of acetic acid and potassium ferrocyanid is dissolved in the same way by heating. The urine gives the biuret reaction. The alcoholic precipitate dissolves in water. In Askanazy's case not only the urine, but the watery extract of the spinal marrow, gave the reactions for this body, though the other lymphatic tumors did not.

The **fever** is to be regarded as belonging to leukemia only during the acute exacerbations, and otherwise must be considered the result of a complication.

One of the most frequent, earliest, and most important symptoms is **dyspnea,** the causes of which may vary. Virchow attributed it to the respiratory incapacity of the blood. More frequently, especially in incipient cases, the cause may lie in the mechanic obstruction to the entrance of air and blood to the lungs. This obstruction is produced by the pressure of a lymphoma on the large blood-vessels, trachea, bronchi, or the lung itself (Trousseau), and may represent a very early symptom. More rarely the dyspnea is produced by lymphomatous tumors in the walls of the respiratory tract (in the mouth, nose, larynx, trachea, bronchi—Virchow), and under these circumstances has several times necessitated a tracheotomy on account of the danger of suffocation. This condition never occurs except within a few days of death, and the operation prolongs life but a short time (Epstein, Mager).

Course.—For a long time (Ehrlich-Dorpat) we have differentiated in the course of chronic leukemia a stage of prodromes and development and a stage of outspoken cachexia. Though a very useful division, it offers no sharply defined time-period on account of the regularly progressive character of the disease. Sometimes the period of development is very protracted; in fact, lymph-gland tumors, present for years and growing slowly, may sometimes represent the beginning of the disease, which is recognized only in a much later stage. As a rule, the spread of the lymphomata advances slowly, and the transition to the cachectic stage which terminates in death, from mechanic obstruction (suffocation) or prostration, is unnoticeable. Yet, not rarely, the transition from an apparently harmless enlargement of the lymph glands to a general leukemic lymphomatosis takes place suddenly, with an explosive-like eruption of lymphatic tumors over the entire body, followed by a normally long, chronic course (Birch-Hirschfeld).

In the further course, which, so far as we know from the cases carefully observed, invariably terminates in death, two varieties are to be differentiated:

(*a*) Death occurs at the end of a protracted course as a natural result of the cachexia or through an anatomic hindrance to life. Yet it is not necessary that the case run uninterruptedly to death. Quite considerable remissions in the general clinical symptoms—in fact, even occasional improvement of the blood-picture—are not rare. Moreover, apparent intermissions, sometimes lasting months, have been described in which complete euphoria returned and the swelling of the lymphatic structures retrograded. True, the blood continues to show, at least in all the cases submitted to our modern technic, a considerable increase in lymphocytes. In the few cases said to have terminated in recovery, the further course is not sufficiently known.

Premature death through intercurrent disease arising on the soil prepared by the underlying process is not at all rare. Among such we must mention the fatally-terminating pneumonias and, as a relatively uncommon complication, tuberculosis.

Death is likewise to be considered premature in the cases in which pressure of the glands or other lymphatic tumors hinders the function of vital organs. This is frequently brought about by the pressure of large mediastinal or other tumors in the region of the head and neck, causing dyspnea by compression of the trachea or obstruction of the mouth and nose, interference with the circulation of the head and the upper half of the body by compression of the large vessels of the chest, or prevention of nourishment by obstruction of the esophagus.

(*b*) Death occurs after an acute exacerbation of the process. The slow process, then (as in pseudoleukemia cases), gives way shortly before death to an acute, often febrile stage, which terminates fatally in several weeks or even days, and presents exactly the same symptom-complex as we saw in acute leukemia.

PATHOLOGIC ANATOMY.

MACROSCOPIC FINDING.

The pathologic anatomy of chronic lymphatic leukemia is exceedingly simple and to a certain extent schematic in its representation. The picture is predominated by the new formation of lymphatic tissue, to which are added moderate organic changes of a degenerative nature, brought about secondarily by pressure and interference with nourishment. The most striking alterations are found, as a rule, in the lymph glands, especially of the trunk (neck and axilla, chest and abdomen). Following these, we have the alterations in the spleen and bone-marrow and the accumulations of adenoid tissue in other organs, especially the

liver. The participation of the lymph structures of the gastro-intestinal tract and the mouth is usually noticeably slight and so unusual that, when it occurs to any marked degree, the cases are considered exceptions and are categorized under the name gastro-intestinal form of leukemia (Béhier).

Nevertheless, small accumulations of lymphadenoid tissue seem to be much more widespread than the naked-eye appearance would indicate; for everywhere, in apparently normal organs, collections of lymphocytes of sometimes not inconsiderable size are frequently found microscopically.

The localization and distribution of the enlarged **lymph glands** conforms to no rule so far recognized, although it is probable that the point of entrance of the excitant or its greatest concentration corresponds with the greatest enlargement. The glands in the region of the neck and head are most frequently enlarged. This is the case in typic leukemia showing a marked lymphocytosis, and much more so in pseudoleukemia, in which the immense enlargement of the glands between the ear and the thorax is almost characteristic.

In cases showing a high-grade lymphocytosis in the blood the glands are usually soft—often almost to the point of fluctuation—have a clear yellowish-gray appearance, and are bound together only by loose connective tissue which is readily broken. Their form is oval or ellipsoid; and they are usually flattened out, though sometimes only on one side, depending on their position and the pressure exercised by the surrounding tissue. Their interior consists of a soft reddish-gray or sometimes whitish-yellow mass, provided no secondary changes, like hemorrhages, have occurred. The cut section is lusterless, wells over the borders, hollowing out in the middle, and gives a readily scraped-off grayish-cloudy juice which sometimes flows in drops. In the pure soft variety no stroma is to be seen. As in the acute form, though much more rarely, hemorrhages are found in the shape of red spots and streaks when the foci are recent, of brownish-red to black-brown spots when old.

The glands are less commonly firm, even to hardness. This variety of swelling is more frequent in pseudoleukemia, under which it will be further discussed.

Spleen.—The spleen is, as a rule, enlarged. There is apparently no simple relation between the blood-finding and the size of the splenic tumor, though the general rule holds that leukemias with a marked alteration of the blood are frequently associated with moderate-sized tumors, while the largest ones are found in pseudoleukemic cases. As

in the lymph glands, so also in the spleen, a soft and a hard variety are to be differentiated. In both we frequently find perisplenic changes when the capsule appears dull white and sometimes irregularly thickened and hardened.

On section, the soft form is yellowish red to brownish red, quite jelly-like in character, and sometimes shows the follicles emphasized when they appear as grayish or reddish-yellow points, enlarged in comparison with the normal. More frequently, however, a sharp limitation of the follicular region from its surrounding is impossible on account of the splenic tissue being riddled with washed-out follicles occurring as specks and streaks, and this diffuse spreading appears even more evidently under the microscope. Hemorrhages around a central white focus are not rare. We frequently find larger, clear, firm nodules with a dark-red halo, consisting for the most part of thick accumulations of lymphocytes.

All transitions between the soft and hard forms are seen. In extreme cases the spleen grates under the knife, and no impression can be made with the finger on the cut surface. The parenchyma is either uniformly brownish red, without distinct follicles, but with a fatty luster on the hard cartilage-like cut surface, interrupted only by the cross-sections of the vessels with thickened walls, or the brownish-red cut surface is riddled with yellowish or whitish specks and streaks, representing enlarged follicles or circumvascular collections of round cells.

When, through secondary causes, a rapid increase in the splenic tumor takes place, the appearance of the organ changes. This is frequently the result of secondary infection or of profuse diarrhea *sub finem vitæ*, and has been attributed, whether justifiably or not, to the effect of the therapy. At any rate, by the simple washing out of the lymphocytes, the spleen becomes rapidly smaller and presents again an entirely normal appearance and consistence.

Areas of softening are rare and are always to be attributed to infectious deposits shortly before death. They are represented by abscesses consisting of the ordinary polynuclear pus-corpuscles.

In addition to the small hemorrhages previously mentioned, large infarcts occur, which are sometimes of sufficient size to be discovered during life (Litten).

Bone-marrow.—Pathologic changes in the bone-marrow are more frequent than in the spleen. A large number, especially of the recent writers, attribute such importance to the lymphatic metamorphosis of the marrow of the long bones that they make the diagnosis of obscure cases dependent on it, and, following Neumann, they even lay the

origin of every leukemia, whether myelogenous or lymphatic, to the bone-marrow. Though this theory would simplify the pathogenesis of leukemia, it can scarcely be proved, as we will see in the discussion of the histogenesis, and, for other reasons previously mentioned, it is not to be considered. The important fact, stated by Neumann with special emphasis, in regard to the exclusive disease of the bone-marrow in leukemia is applicable particularly (as Walz insists) to acute leukemia. The history of Neumann's case, which seems to have been an exception, of Browdowski's and, possibly, of Waldeyer's, or of any recent case (for instance, Pappenheim's) is not sufficiently known to pass a verdict on the duration of the leukemia before the beginning of observation. Moreover, in chronic leukemia we have seen the swelling of the spleen and glands disappear; consequently we have no reason to suppose that the same mechanism could not produce such a rapid discharge of newly-formed cells that any gross swelling would be prevented from the beginning (see p. 564). Further, that only the bone-marrow should be found decidedly abnormal in these cases is not so striking. In lymphatic leukemia we see all the blood-making organs transformed into manufactories for lymphocytes. This transformation in the general lymphatic apparatus is only one of degree; in other words, is scarcely more than a simple hyperplasia (true, more evidently so in the lymph glands than in the spleen), an internal metamorphosis recognizable in the lymph glands by obliteration of the difference between the proliferating central and the quiescent marginal zone (see pp. 564, 601). In the bone-marrow, however, the lymphadenoid hyperplasia represents the development of a tissue, which ordinarily stands in the background—it represents, in fact, the development of an entirely new tissue, and so it is readily recognized. The second argument for the importance of the bone-marrow—namely, that it is invariably affected, is not objectionless, since isolated cases (especially that of Fleischer and Pentzoldt) are known in which no abnormality was found and the positive findings, though numerous, are not yet convincing. True, these negative cases were not subjected to all the demands of our modern technic, and it is possible that on a more careful examination abnormalities would have been found.

[Rosenfeld[1] reports 3 cases of chronic lymphatic leukemia, and believes that the disease was primary in the lymphatic glands, with secondary metastasis to various organs in 1 of his cases. He thinks the evidence is against a primary myelogenous origin of lymphatic leukemia, and that the bone-marrow was certainly secondarily involved in

[1] *Zeit. f. klin. Med.*, Bd. xlii., h. 1 and 2.

2 of his cases. His general view of leukemia is that it is a widespread lymphosarcomatosis with varying symptoms, according to the parts affected. The morphologic distinction of lymphemia and myelemia must be accepted only up to a certain point. The large lymphocytes in Fränkel's acute cases would have been attributed to the bone-marrow, according to the morphologic method of study.—ED.]

The bone-marrow in lymphatic leukemia presents a picture which Neumann has described so thoroughly under the name of lymphadenoid transformation that we can not do better than repeat his own words:

"The color fluctuates between red and gray in the most varying transitions and combinations. The consistence is sometimes soft like jelly, again quite hard like a succulent lymph gland. The tissue is held together much more firmly than in the previous cases (that is, of 'pyoid' metamorphosis in myelogenic leukemia), so that I found the marrow easier to harden in chromic acid and alcohol, and easier to bring into a suitable state for cutting microscopic sections than under the ordinary pathologic and normal conditions. There was, consequently, no difficulty in convincing ourselves that we had to do with a tissue which resembled closely the adenoid or reticular tissue of lymph glands. Lymphoid cells, usually of the small variety, so far as our observations extended, lay thickly massed in the meshes of a fairly thick irregular reticulum, which contained numerous oval, clear nuclei provided with nucleoli, and these nuclei were distinguished from those of the lymph corpuscles by their greater size and lusterlessness. The vascular apparatus, so far as could be seen without injection, showed capillaries of a smaller diameter than in the ordinary red marrow. Their walls were occupied by the same large oval, clear nuclei as were found in the reticulum, and were bound to the latter by fasciculi which were inserted sometimes into the nuclear portions of the vessels and again passed over into fine anuclear thread-like prolongations of the vessel wall."

In general, a red to dark-red color prevails in the marrow of the tubular bones. It is readily translucent, of a gelatinous consistence, and is appropriately described by the term raspberry-jelly-like.

The marrow of the short and flat bones is usually unaltered to the naked eye, though it sometimes inclines to a brick-red or brown color.

The marrow spaces are usually, even if often only slightly, distended. The cortex of the bones is riddled in places by dilated canals, from which the marrow seemingly wells out and produces nodular masses between the periosteum and the bone. Whether the condition of osteosclerosis, which has been described rarely in myeloid leukemia (Henck)

and in some lymphatic hyperplasias of the bone-marrow (multiple myelomata [Kahler, Hammer, v. Baumgarten], lymphosarcomatosis [Türck]), occurs also in lymphatic leukemia, is not known.

In addition to these three organs (lymph glands, spleen, and bone-marrow), particularly known as lymphocyte builders, metastatic accumulations are found in almost all the organs. These so-called metastases are not the result of the deposition of displaced parts of tumors, as are the metastases of malignant tumors; in fact, this designation has been adopted merely on account of its readiness and easy intelligibility.

Liver.—Such scattered lymphomata are almost constantly present in the liver as very small to hazel-nut-size nodules and streaks, usually yellowish white in color and situated on the surface and in the interior of the organ. As we shall see later, microscopic examination shows them surrounding the branches of the portal vein. Besides these lymphatic deposits, we find only slight degenerative changes, as fatty degeneration of the marginal parts, and moderate pigmentation. The whole organ is frequently enlarged, though usually only moderately, and but rarely to a high degree.

Kidneys.—The conditions in the kidneys are very similar. The same whitish nodules and streaks are seen, made up of lymphocytes deposited in the circumvascular connective tissue and between the tubules of the kidney parenchyma. The parenchyma is usually unaltered and shows no signs of degeneration. Inflammation of the kidney, as mentioned in the clinical part, is rare, yet acute hemorrhagic nephritis sometimes occurs. Uric-acid infarcts have been described but seldom.

The **mucous membranes** usually show slight changes. The most frequent of these is lymphoid enlargement of the tonsils and, considerably more rare, swelling of the nasal and pharyngeal mucous membrane. The leukemic collections in the larynx and the trachea occur either as nodules in the mucous membrane, which under the influence of trauma and infection may ulcerate, or as a diffuse raised infiltration of the false vocal cords (leading sometimes to obstruction of the respiratory tract) and of the deeper parts of the larynx and trachea. They rarely affect the epiglottis and true vocal cords. The leukemic process in the larynx is very frequently complicated by ulcers in the region of the vocal cords, which, by a widespread necrosis of the cartilage, penetrate through to the pharynx (Mager). Hemorrhages have been observed several times, edema of the glottis never.

The rest of the **respiratory tract** shows but little tendency to

leukemic lesions. In the same way the entire **gastro-intestinal tract** shows but slight changes (swelling of the follicles, necroses, and ulcers), and then only in the cases which become acute near the end of life.

Skin.—The leukemic tumors of the skin present moderately sharply circumscribed nodules with a uniform grayish-red to whitish cross-section, which clearly resembles that of the lymph glands in luster and color. The other leukemic changes in the skin, post mortem, show nothing remarkable to the naked eye.

In the **nervous system** lymphomata are observed, especially in the peripheral nerves. They occur most frequently in the region of the cerebral nerves; thus, lymphomata have been described about the optic nerve, causing protrusion of the bulb (Birk), about the branches of the trigeminus, the facial and acoustic nerves. At these sites we find degeneration of the nerve fibers, partly due to the pressure of the lymphoma, partly to causes so far unknown.

Lymphomata have practically never been observed in the brain and spinal cord. Yet isolated areas of softening and degeneration have been encountered, especially in the bulbar region, which were produced sometimes by the pressure and the consequent nutritive interference of neighboring (meningeal) lymphomata, again without known cause.

Lymphomata are more frequent in the cerebral and spinal membranes.

The middle and internal ear, according to Schwabach, are often the seat of lymphatic accumulations and hemorrhages.

HISTOLOGIC FINDING.

The uniformity of the anatomic changes becomes most apparent under the microscope. The fundamental microscopic structure consists at first of a circumvascular collection of lymphocytes, which later takes on a tumor-like appearance (hyperplasia). Under certain circumstances we have, too, an increase in the connective-tissue stroma (sclerosis), which works against the lymphocytic increase and may, in places, lead to destruction of the lymphatic parenchyma.

In the **lymph glands** we find greater and smaller masses of regularly round cells corresponding to the medullary columns and cortical nodules, though usually much larger. In their internal structure these columns and nodules often resemble the normal so closely that the proliferating center may be distinguished from the peripheral quiescent zone (Bizzozero). Yet, possibly, the difference between the large-cell proliferating center and the small-cell border zone is more frequently

obliterated, and we have one mass of uniformly small mononuclear cells, as in a quiescent gland (Pinkus).

The cells consist of a round nucleus which stains intensely with hematoxylin and basic anilin dyes and which contains a number of large dark chromatin granules, connected with one another by fine chromatin threads. These large granules are arranged especially about the margin, though a few are found in the center. The substance between these chromatin filaments remains almost unstained. The nucleus is usually situated a little excentrically in the small ring of protoplasm which represents the cell body. In sections hardened in alcohol the cell body stains but feebly with acid and almost not at all with basic dyes, and is usually extended into irregular, jagged prolongations in the form of a star. It seems to consist of a thick filamentous network. No granulations have been found in it.

Statements differ as to the degree of increase of these lymphocytes. While an increase in mitoses has been asserted now and again (Bizzozero), they are frequently found wanting, possibly as a result of the proliferation ceasing at the time of death (Pinkus). It appears as if the assertions in regard to the increased formation of lymphocytes represented the histologic findings of intra-vitam extirpated glands rather than of glands removed post mortem. We have absolutely no ground at present for the assumption that when no mitoses are found the increase of cells has occurred in an amitotic way.

Apart from the reticulum and the vessels, we find almost nothing else between the lymphocytes. Polynuclear leukocytes are no more frequent than in any other non-inflamed tissue, and mast cells are rare, yet eosinophile cells are sometimes strikingly increased, especially in cases of pseudoleukemia.

The interstitial connective tissue is represented in the soft lymphomata by a scanty normal tissue which carries the nerves and lymph and blood-vessels, and surrounds the lymph sinuses. From this proceeds the delicate meshwork in which the lymphocytes are imbedded. The lymph vessels, especially the large cortical sinus, are filled with lymphocytes, isolated polynuclear leukocytes, and large cells with heterogenous protoplasm, called phagocytes, which apparently serve for the absorption and destruction of white and red blood-corpuscles.

Spleen.—The structure of the spleen simulates much more than normally the histologic picture of a lymph gland. The lymphatic constituents are predominant. The whole organ, which is normally closely allied to the structure of a lymph gland, is transformed into a conglomerate lymphadenoid mass. It is made up of larger and smaller accu-

mulations of lymphocytes, between which lie the stroma, the vessels, and the sinuses of the spleen. This interstitial tissue is scarcely increased above the normal, and, therefore, in comparison with hyperplastic lymphoid pulp, appears decidedly in arrears.

According to the variety of the splenic tumor (hard or soft), the trabecular connective tissue may be either increased or not. Yet even in the hard form we never find a marked increase, since the lymphocytic parenchyma always predominates. The vessels are, in general, well filled with blood and show considerable numbers of the large corpuscle-containing cells, to which we have previously called attention in the lymph glands under the name of scavenger cells.

Bone-marrow.—Among the constituents of the bone-marrow, all are decreased except the lymphadenoid, which is normally least noticeable. This is increased to such an extent that the lymphocytes exceed in number all other cell varieties. The parenchyma is composed almost exclusively of ordinary red blood-corpuscles and lymphocytes (see p. 597). Nucleated red blood-corpuscles, otherwise very frequent, are in outspoken cases almost entirely wanting; the advanced stages of the neutrophile cells of the blood and the giant cells of the bone-marrow are lessened in number. The lymphocytes filling the marrow spaces are exactly the same as those described in the lymph glands and show a round granular nucleus with a small amount of protoplasm. They form a compact uniform mass, which wells through all the openings of the bone, overflowing, as it were, the narrow confines of the marrow canal. Thus, large lymphatic nodules are formed under the periosteum, and the canals from the central marrow cavity to the subperiosteal space become dilated.

The histologic picture of lymphomata in other organs closely resembles that already described in the lymph glands. In the follicular organs (mucous membrane of the mouth and of the gastro-intestinal tract) we often find obliteration of the boundaries of the follicles and absence of the proliferating centers. We see then a continuous connection of the increased reticular tissue, which normally may be unnoticeable, as well as an increased number of foci containing round cells imbedded in the meshes of the delicate reticulum. The round-cell accumulations in atypic localities are also like the ordinary.

Such accumulations of lymphocytes are found in almost all cases in the **liver**, and somewhat less frequently in the **kidneys**. In these organs we have to do with a simple accumulation of lymphocytes lying in the well-known reticulum made up of cells with large nuclei. In the liver they are located in the connective tissue which, with the branches of

the portal vein, surrounds the acini, and display the widest differences in size—from a simple infiltration of several cells to nodules the size of a hazel-nut. From the margins of these lymphomata, diffuse prolongations extend on all sides into the acini and between the columns of liver cells.

In the **larynx** and **trachea** the lymphocytic infiltration lies in the mucosa and submucosa and, by predilection, about the mucous glands; in the beginning about the secreting parts; later about the excretory duct also.

The leukemic tumors of the **skin** lie in the cutis and in the upper part of the subcutaneous tissue. Moreover, we find lymphatic tissue not alone at the site of the tumors, but about them (though separated), in the shape of small microscopic accumulations of lymphocytes. In fact, even in the healthy skin of certain parts of the body we see the same as a sign of the widespread distribution of the leukemic deposits. This disease of apparently healthy parts, which we have already recognized in other organs, especially the liver, is plainly demonstrable in the skin. The appearances in this organ are very important, for the reason that it is the only one in which an anatomic examination may be made with readiness during life—in other words, during the different stages of development of the disease.

The leukemic infiltration of the skin begins with a circumvascular accumulation of lymphocytes. The deep coils of the sweat glands seem to be the favorite sites of origin. From here the lymphocytic tumor spreads toward the subcutaneous tissue and the epidermis. The infiltration usually remains separated from the epidermis by a small layer of free cutis, and only rarely pushes upward around the gland duct to the epidermis. It penetrates the deeper tissues, the subcutaneous fat and the musculature (between the bundles of which it terminates), first in columns, later in diffuse masses. All the tissues of the affected part are surrounded by the round cells, though they are not destroyed. The lymph vessels in the vicinity are sometimes filled with lymphocytes, which would go to indicate that the specific cells gain entrance to the circulation even from these lymphomata. Further, if we may judge from the conditions seen, it would appear that in isolated cases the skin symptoms preceded the general lymphatic disease—in other words, that the skin was the starting-point of the leukemia. This observation has led to the differentiation of a cutaneous form of leukemia. This form is not, however, identical with the lymphadénie cutanée of Ranvier-Cornils, which is usually a mycosis fungoides. The question of the skin as the starting-point of the leukemia is of quite as

little importance as that of the bone-marrow or lymph glands. Since we regard lymphatic leukemia as the result of a predisposition to growth of all the lymphatic tissues, no matter where situated—whether in previously developed lymphatic organs or in the interstitial connective tissue, and not as a disease of some particular lymphatic tissue with subsequent metastasis after the fashion of a malignant tumor—it is absolutely indifferent to us whether this or that organ first becomes perceptibly diseased. We know that lymphatic tumors may be widely distributed through the body without giving rise to clinical symptoms; we know further that the size of the tumor does not always correspond to its age, for we see extraordinary fluctuations; in fact, there may even be retrogressive changes in individual organs which previously showed a marked increase in size.

In a number of cases the histologic structure of these skin lymphomata is exactly like that of lymphodermia perniciosa (Kaposi), which is identical with the érythrodermie mycosique of the French. In another series of cases, however, the histologic structure is not lymphadenoid, but a sort of granulation tissue, consisting of spindle, round, plasma, and mast cells. Whether the tumors occurring in this affection are to be considered as mycosis fungoides, as has been suggested, must be left for future investigation to decide.

The pathologic anatomy of the remaining skin lesions (usually urticarial in character) corresponds, at first, to that which they show under other circumstances. We have to do with circumscribed exudations. They are particularly marked in the epithelium, which they transform into vesicles by an intercellular exudation. The reaction of the cutis is usually slight and is expressed by a moderate circumvascular round-cell infiltration. Still, we sometimes see, in addition, a large emigration of ordinary and eosinophile pus cells from the cutaneous vessels into the vesicles. Later on, small granulation tumors composed of round and spindle cells, with here and there an isolated Langhans' giant cell, sometimes develop at the site of the scratched and cicatrized vesicles.

The changes in the **nervous system** and the organs of special sense appear, microscopically, as a mixture of lymphocytic infiltration and hemorrhage followed by the formation of scar tissue and by degeneration processes, especially fatty. As in all other organs, the lymphatic infiltration occurs here in small, irregularly distributed foci. Genuine lymphomata are rare and are limited (Eichhorst) to the membranes and the peripheral nerves, with a predilection for the cerebral nerves. Hemorrhages and their results are observed especially in the

eye. The white center frequently found in them represents a lymphocytic accumulation. The symptoms of retinitis leukæmica are expressed histologically by lymphatic infiltration and fatty degeneration of the nerve fibers. Hemorrhages and lymphatic infiltration constitute, likewise, the basis of the diseases of the ear (Schwabach). Still, in a few cases belonging to this category the significance of the cicatricial processes especially may be doubted, inasmuch as they have been found as the result of previous disease and not of the leukemia (Gradenigo, Kümmel). Degeneration (swelling and breaking up) occurs in the fibers in the spinal cord (Nonne), the medulla oblongata (Kast), and in the brain, as well as in the peripheral (especially cerebral) nerves.

HISTOGENESIS.

In the discussion of the pathologic anatomy we saw that accumulations of specific cells occurred not only in the lymph glands—the principal source of lymphocytes—and the other leukocyte-making organs (spleen, bone-marrow, tonsils, lymph nodules), but also in many other parts of the body where only the merest traces of lymphadenoid tissue are normally found. True lymphatic tissue is widely distributed through the healthy body, and is by no means limited to the grosser nodules (lymph glands and follicles). The whole body is encompassed by a net of lymphatic tissue winding through all parts, and, though usually present in but small amounts, it is here and there collected into larger masses, from which the normal requirement of lymphocytes is supplied by cell proliferation. Nevertheless, the readiness with which a quiescent is converted into a proliferating focus is seen in every inflammation in which an immense round-cell infiltration arises from small traces of lymphadenoid tissue. Moreover, this proliferation does not stop at an enlargement of the individual focus, but frequently throws an excess into the lymph circulation. The formation of lymphocytes, therefore, is to be considered as a normal function of every part of the body in response to so-called inflammatory irritation. This property of lymphoma development in any part of the body stands in sharp contrast to the likewise ubiquitous inflammatory symptom of suppuration, since the cellular elements of the latter (the polynuclear pus cells) do not arise *in loco*, but only in one system of organs—namely, the bone-marrow—whence they wander into the blood-vessels and, carried by the stream, escape through the vessel wall at the site of irritation.

In leukemia the behavior of these two very different tissues (the lymphocytic and the specific bone-marrow tissue) corresponds exactly with the normal.

That the bone-marrow tissue produces the principal portion of the leukocytes found in the blood in myeloid leukemia is generally acknowledged; that the secondary leukemic tumors of the internal organs in the same disease arise metastatically by transplantation of the marrow tissue at the sites of secondary tumor formation is, at least, very probable, since under normal conditions the occurrence of proliferating myeloid tissue outside the bone-marrow thus far has never been observed.

In contrast to this metastatic genesis of the myeloid-leukemic tumor stands that of lymphatic leukemia, which, exactly like the inflammatory lymphocytic infiltration, is built up from lymphatic tissue normally present at that particular part of the body. In other words, all tissues are interwoven by a lymphadenoid network in which larger lymphomata may be developed.

Lymphocytes are undoubtedly carried into the blood, by way of the lymph vessels, from the hyperplastic lymphadenoid bone-marrow, from the likewise hyperplastic spleen, from the lymphomata in the skin, from the diffuse lymphocytic infiltrations in the liver and kidneys, and from all the other locations of lymphocytes, as well as from the lymph glands. The proof that all these lymphomata discharge lymphocytes into the blood in this way is shown by the fact that the lymph vessels near them are found filled with lymphocytes, as is the case, under normal conditions, about the lymph glands (Pinkus).

In order to explain the peculiar fact that in apparently similar cases there is sometimes a normal proportion of white and red blood-corpuscles (pseudoleukemia), and, again, a considerable abnormality (lymphatic leukemia), many theories have been suggested. We shall take up here only the one proposed by Neumann, which is the most generally known and has stood best the test of time. According to this theory the lymphadenoid transformation of the bone-marrow must be regarded as an essential in the origin of lymphatic leukemia. This is supported by the fact that disease of the marrow is found in every case of lymphatic leukemia, and in some exclusively. With slight modification, but more clearly, Pappenheim expresses this theory in the words: "If the excitant affects first, and exclusively, the spleen or the lymph glands (the distensible capsules extending with the growth), only pseudoleukemia results; but if the bone-marrow is attacked and becomes hyperplastic, then leukemia ensues."

Simple as the conditions are made by this explanation, several circumstances prevent us from accepting it (see pp. 598, 599). We have mentioned that the cases of lymphatic leukemia with exclusive disease of the marrow all come under the head of acute leukemia, and

also that in these acute cases we have not sufficient evidence to prove that the non-enlarged lymph glands do not participate in the lymphocytosis, since they show all the signs of a very high degree of proliferation. Further, the view that cases of generalized lymphomatosis show no blood-changes does not correspond to the facts, for we find in them a completely similar, even though only a qualitative, alteration of the blood. Absolute differentiation between lymphatic leukemia and pseudoleukemia, therefore, falls to the ground. Moreover, as suggested before, we have direct proof that lymphomata, other than those of bone, discharge lymphocytes into the blood.

Further investigations directed especially toward the participation of the different organs in the lymphocytosis are necessary in order to explain these difficulties.

Among the frequently mentioned possibilities—(1) that the lymphomatous masses represent deposits from the blood in which the lymphocytes increase partly by cell division, partly by prevention of their (normal) metamorphosis into red blood-corpuscles or polynuclear leukocytes; (2) that the lymphomatous masses, while not deposited *in toto* from the blood, develop at these sites from metastatically carried cells; and (3) that they arise as a result of a general predisposition to the new formation of lymphadenoid tissue from small accumulations of this tissue normally present in these localities—the last is the only one so far demonstrated.

The old assumption which attributed the origin of the lymphemia to the failure of the transformation of lymphocytes into polynuclear leukocytes must be rejected, since, as Ehrlich has shown, we have to do here with two very different histologic sources—the source of the lymphocytes and that of the neutrophile bone-marrow cells—which have nothing in common with and never go over into one another. On the contrary, it may be regarded as proved that the lymphocytosis is dependent on an increased formation of lymphocytes in the lymphomata and the discharge of these cells into the blood, a process which can be seen in its different stages under the microscope.

Possibly a lessened consumption of lymphocytes may prove a factor in addition to the increased formation. This assumption is supported by the fact that only very few mitoses are found, at least after death, in the lymphomata of chronic lymphatic leukemia. Still, apart from the possibility that this small number of mitoses may be the result of death, dependent perhaps, in part, on the technic of the examination (especially since other observations assert numerous mitoses), this assumption is apparently contradicted by the direct evidence in the

blood of a very considerable destruction (Gumprecht) or, at least, liability (Askanazy) of the lymphocytes. The determination of this point must be left for the future. It would be well if in future investigation special attention was directed to comparison of the number of degenerated lymphocytes in the blood with the mitoses in the lymphatic organs, and, when possible, to comparison of the mitoses found during life (in lymphomata removed intra vitam) with those found in the organs of the same person post mortem.

Sufficiently conclusive investigations are still wanting in regard to the histogenesis of another peculiarity of lymphatic leukemia—namely, the frequent sudden retrogression of the lymphomata and the lymphemia. Whether the destruction of the cells takes place at their site of origin or only after their passage into the blood is a question which has not been determined. This phenomenon is to be placed in line with the disappearance of other neoplasms, especially certain round-cell tumors occurring in the skin, known under the name of sarcoid tumors (so-called multiple skin sarcomatosis, mycosis fungoides), in which a partial or sometimes complete retrogression has been observed, either spontaneously or under the influence of arsenic.

ETIOLOGY.

Even in prebacteriologic times the cause of leukemia and pseudoleukemia was frequently suggested to be some infectious agent which first set up a local injury at the point of entrance, or which forced itself into a diseased organ (for instance, an enlarged tonsil or tonsillar abscess, or protracted ulcer of the gums as a result of carious teeth) and was afterward distributed throughout the body. Later, bacteria were repeatedly sought as the cause, and now and then found. Though these investigations were not limited to the ordinary pyogenic and similar commonplace infectious bacteria to which there was no possibility of attributing an etiologic significance, none of them could be demonstrated to be the etiologic agent; on the contrary, they all proved to be accidental contaminations or the causative agents of complications (for instance, tuberculosis).

In late years several communications have been made which seem to support the occurrence of animal parasites. Such forms were observed in the fresh blood of lymphatic leukemia by Mannaberg. They were later observed by others, though their significance as parasites was left undecided by some, and contradicted by Strauss and Pollmann. A new phase of this question was brought up by the

studies of Löwit, who demonstrated peculiar organized ameba-like forms in the white blood-corpuscles of both kinds of leukemia. The greater part of Löwit's investigations were limited to the etiology of myeloid leukemia. Yet even in the blood and certain blood-making organs (spleen and bone-marrow) of lymphatic leukemia he found forms which he described (true, with a certain amount of reserve) as ameba-like bodies under the name hæmamœba leukæmiæ parva (vivax).

[Türk,[1] in discussing Löwit's theory of the amebic etiology of leukemia, concludes that the supposed parasite of myelogenous leukemia of Löwit is not a parasite and not even a preformed structure in the blood, but an artifact formed out of the mast-cell granulations. The supposed transmission of the disease to animals, reported by Löwit, is questioned as doubtful.—Ed.]

Further investigation must be undertaken to establish the value of Löwit's assertions. So far the subsequent investigators have unexceptionally taken the opposition (see p. 648). We will detail in short the finding as Löwit describes it in his book.

The organisms demonstrated by special staining methods[2] are seen as small forms which frequently possess spur- or hook-like processes, and sometimes show a nucleus-like body interiorly. Löwit endeavored to show a course of development for those bodies in which he differentiated:

1. Young forms, which occur alone or, more frequently, several together in a lymphocyte.

2. Growing forms, larger than No. 1, and showing karyokinetic figures.

[1] *XVIII. Congress f. Innere Med.*, 1900, p. 251.

[2] They stain dark, metachromatic violet to reddish brown by the following method: Fix on Ehrlich's copper plate; heat the preparation gently in a watch glass full of old Löffler's methylene blue; allow to stand till cool (five to ten minutes); wash in water; differentiate in 0.3 per cent. hydrochloric acid in alcohol; wash in water; dry; mount in balsam. Fixation by alcohol and ether is to be avoided, since the organisms stain poorly after contact with alcohol. Similar results are achieved, without warming, with thionin, which may be combined with a triacid stain, the differentiation with hydrochloric acid alcohol being omitted. In the examination of histologic sections the hardening must be done by alcohol and bichlorid of mercury; solutions containing chromic acid or formalin are not adapted. The stain recommended for sections is a mixture of Löffler's methylene blue, 30 parts, and concentrated watery solution of thionin, 15 parts. Stain for fifteen to twenty minutes with gentle heat, differentiate in 0.3 per cent. hydrochloric acid in alcohol, treat with alcohol, 96 per cent., then with xylol, which clears after drying the preparation several times in the air, and mount in Canada balsam. Still better results are obtained by staining for twenty to twenty-four hours in saffranin (watery alcoholic solution), which stains the ameboid bodies rust brown to brownish red, and the rest pale or red, the basophilic granules a faint-yellowish red, the products of nuclear degeneration more or less dark red.

3. Sporulation forms, which recall the sporulation forms of the malarial parasite.

4. Degeneration forms, irregular granules and clumps, which, nevertheless, stain like the other forms.

These bodies are found but rarely in the circulating blood, but are more frequent in the internal organs, where they occur in isolated places in numbers. It is noteworthy that they are less frequent in the lymph glands than in the spleen and bone-marrow. Injection into animals, which, according to Löwit's assertions, succeeded with the corresponding forms in myelogenic leukemia, was not successful in lymphatic leukemia.

The determination of all these points must be left to the future, for it is still a question whether these bodies represent unicellular organisms or only peculiar products of cellular degeneration. Löwit[1] himself considers it impossible that these bodies are the products of lymphocytic degeneration produced by hyper- or hypochromatosis with karyorrhexis or karyolysis, since such products do not stain metachromatically by the method described, and the hemamebæ are scarcely more than suggested by the ordinary stains by which degenerations are brought out.

Granting all this, the question still remains whether these forms, even though they occur only in leukemic blood, are to be considered the cause of the disease. In this regard the finding of myelogenic leukemic amebæ in one case of lymphatic leukemia which was characterized by containing a large percentage of Ehrlich's myelocytes is striking, for, according to our conception of the different forms of leukemia, this finding alone would be sufficient to show a myelogenic-lymphatic mixed form. It is further remarkable that the ameboid forms, even in myelogenic leukemia, are found especially in the lymphocytes, the cells least characteristic of leukemia.

If we look at the etiology from the standpoint of infection, the accurate determination of this point of view being left to the future, we have at once certain things cleared up in the origin of the disease. In this regard those cases are especially significant in which lymphatic leukemia followed an irritation of the lymphatic tissue. True, the information derived from the most frequent group of these cases (lymphodermia perniciosa) is not great. Our knowledge of the histologic changes (especially in the internal organs) at the beginning is too limited, since the positive diagnosis can be made only in later stages. The frequency of the combination of these widespread erythrodermias with subsequent lymphatic leukemia indicates the necessity of the most

[1] *Verhandl. der Cong. f. innere Med.*, 1899 and 1900.

careful clinical and hematologic examination of suspected cases. Several cases of leukemia in connection with sarcoma seem to offer more information. Still, it is doubtful if the process in these cases is as simple as has been commonly considered to have been in Lücke's well-known case, in which the leukemia was attributed to the passage of the blood through a lymphosarcoma developing in a blood-vessel. Neumann's previously mentioned explanation is more intelligible. This attributes lymphatic leukemia to specific irritation of a hyperplastic bone-marrow like that which seems to occur in cases of acute lymphatic leukemia following a severe anemia (Strauss).

DIAGNOSIS.

The diagnosis of lymphatic leukemia can be clinically assured only through the *finding of the specific (lymphatic) blood-picture.* Large lymphomata, a splenic tumor, an inclination to hemorrhage, associated with the affections of the skin which we have described (urticaria, erythema, tumors), suggest the diagnosis and call for a blood-examination. In a certain number of cases of pseudoleukemia the only objective differential sign is the degree of the blood-alteration, since all the other symptoms are common to both diseases, and even the blood may undergo qualitatively similar changes.

The blood-picture, therefore, remains the most important and significant differential symptom, since all the others can only make the diagnosis probable but not positive.

The differentiation of pseudoleukemia from diseases similar to it will be discussed in the next section (p. 625).

When a marked increase in leukocytes has determined the existence of a leukemia, the differentiation of lymphatic from myeloid frequently can be made, at least with a certain degree of probability, from the gross clinical symptoms. Thus, for example, the unique enlargement of the spleen in myeloid leukemia, in which the organ takes up one-half to three-quarters of the abdominal cavity, presents frequently a characteristic picture which is in sharp contrast to the marked diversity and distribution of the pathologic changes in lymphatic leukemia, with its usual enlargement of all the lymph glands, its absence of bone-marrow symptoms, its atypically localized tumors in the external and internal organs, and eventually its more rapid course. Yet this probability becomes positive only through the microscopic finding, which was described so well by Virchow in fresh blood, and is so readily demonstrable by Ehrlich's methods. In this case the characteristic variegated

blood-picture of myeloid leukemia stands in contrast to the simple increase in lymphocytes of lymphatic leukemia.

PROGNOSIS.

Chronic lymphatic leukemia must be considered a fatal disease. Its duration fluctuates within very considerable limits. It may prove fatal in several months or may last as many years; but it seldom lasts more than a year after the evident appearance of the cachectic stage. During its course marked and long-continued remissions occur, sometimes spontaneously, or, again, as the result of intercurrent disease or therapy. The few reports of complete cures are rendered doubtful by the uncertainty of the diagnosis, which up to very recent times was not established with sufficient accuracy. Moreover, the observations in these cases were not carried on for a sufficiently long time, and this gives ground for the objection that the supposed cures were only transitory remissions. This last conclusion is supported by the frequent report that cases of pseudoleukemia which were considerably improved by arsenic eventually succumbed after a period free from symptoms, careful observations usually not having been made, though sometimes they exhibited an outspoken relapse in the form of a frank lymphatic leukemia.

Since, therefore, the principal characteristic of lymphatic leukemia is the lymphemic blood-picture, the prognosis in a case of lymphatic tumors becomes at once unfavorable as soon as an increase of lymphocytes becomes evident in the blood.

We have already discussed the manner of death when speaking of the course of the disease.

TREATMENT.

The medical treatment of chronic lymphatic leukemia is almost limited to mitigating the objective symptoms and improving the subjective feelings, since an actual influence on the duration of the disease is rare and an averting of the fatal termination has never been accomplished.

The simple surgical procedure of removing all the diseased parts is impossible. Partial extirpation is sometimes indicated on mechanic grounds. This indication is seen especially in the cases with large tumors and but slight blood-change (in other words, in pseudoleukemia as we understand it). Sometimes it is the dyspnea, produced by a lymphoma of the neck, which calls for the operation, again symptoms

caused by an enlarged spleen. A lasting effect has never been obtained by extirpation of the glands, though the operation is often astonishingly easily done and very well borne. Extirpation of the spleen offers a much better prognosis in pseudoleukemia than in genuine leukemia, although in either case death almost regularly follows within a few months Operative interference in cases showing marked alteration of the blood is practically always contra-indicated on account of the immediate danger of fatal hemorrhage, and because the temporary effect produced is often followed by a rapidly progressing development of the process.

Still, it is advisable not to put off too long the extirpation of isolated, long-persistent glandular tumors of unknown origin which neither advance nor retrogress, provided there is the slightest reason to suppose that they may represent leukemic tumors.

Among the external remedies, different preparations of iodin have been employed. Good results have been occasionally seen after the application of iodoform (Moleschott, in whose case there is some doubt as to the correctness of the diagnosis; Fleischer and Pentzoldt), possibly as a result of the persistent diarrhea produced. The spleen has been made smaller by the application of an ice-bag to this region, though no further influence on the disease was manifest.

After it was observed that a considerable decrease in the lymphomata and the lymphemia sometimes follows acute infectious diseases (for instance, cholera, and especially erysipelas), inoculation experiments were tried as a therapeutic measure. The results of the erysipelas injections are not encouraging, especially when the dangers are taken into consideration. It is worth noting that failures have been reported, both after the inoculation of streptococcic cultures and erysipelas masses themselves (Mager). Moreover, even intercurrent infectious diseases have shown no influence (Hirschlaff).

Next to these inoculation experiments stand the injections of organic metabolic products, which have been several times employed with a certain amount of success. Their influence on the lymphemia, and simultaneously on the whole disease, has been considered analogous to their well-known influence on leukocytosis (milk extract, Jacob; spermin, Richter; tuberculin, nuclein, Pal). The diminution obtained in the leukocytes was always only transitory. Nevertheless, since a certain diminution in the number of white blood-corpuscles always takes place, these attempts can not be considered as absolutely useless.

Among the internal remedies, the preparations of iodin (especially iodid of potassium) must be mentioned, on account of the wonderful

cures of generalized lymphomata ascribed to it in earlier communications. Mosler saw apparently complete cure following quinin in 1 case, though the diagnosis is not beyond cavil. These two remedies are, however, generally used only as diagnostic aids in the differentiation of syphilis and malaria.

The only drug which has achieved decided success in a number of cases, especially those with large lymphomata and a slight lymphemia, is arsenic. The results of arsenic treatment are in the beginning usually good. But, unfortunately, a relapse almost always comes on which the arsenic can not influence, and so the fatal termination is only postponed, not prevented (Bramwell).

The arsenic is administered in various ways, which will be more thoroughly discussed in the article on pseudoleukemia.

In pills it is employed in the form of the old Pilulæ Asiaticæ with Piper nigrum, or, better, with sodium carbonate:

℞	Acid. arsenios.	0.3;
	Sodii carbonat.	1.0;
	Pulv. radic. liquir,	
	Succ. liquir	āā 5.0;
	Glycerin	gtt. ij.

M.—Ft. mass pilul. e qua form. pilul. No. C.
Sig.—Begin with 2 pills daily and increase to 6 or more.

Fowler's solution may be given three times daily, increasing, 1 drop a day, from 3 to 15 drops; or sol. acid. arsenios. 0.25 : 50.0 three times daily, increasing from 3 to 30 drops. The increase should always be slow. If no symptoms of poisoning appear, the high dose may be continued without any decrease. Sudden cessation, unless forced by acute symptoms of poisoning, is to be strictly avoided. Such cessation often causes irreparable damage, through the development of a severe cachexia. Therefore, in case the arsenic is to be dropped from the therapy, let the decrease be gradual even when no great care was exercised in the increase.

More exact doses, with greater effect, can be obtained from the employment of subcutaneous and intravenous injections, and they are frequently better borne. The latter are especially recommended for large doses. They should be introduced in a superficial vein of the elbow, with a sterile syringe, after most careful cleansing of the skin with soap, ether and alcohol. It is well to employ a large syringe, and, by sucking up some blood before injecting, convince ourselves that the needle is in the lumen of the vessel. For subcutaneous injection a modified Kōbner's solution is to be recommended, in which the addi-

tion of cocain prevents the burning sensation usually experienced for about fifteen minutes after:

℞	Sodii arsenitis	0.1;
	Cocain hydrochlorat.	0.3;
	Aqua destillat.	ad 10.0.
M. D.—Sterilisa.		

Of this 0.5 to 2 c.c. are injected daily, and, when well borne, still larger doses. For intravenous injection the addition of cocain is unnecessary, and so the pure Köbner's solution is employed. The most careful-sterilization of the injection fluid is naturally an absolute essential.

The intraparenchymatous injection of arsenic solution, as recommended by Billroth and Winiwarter, is sometimes even more effective.

Any of these measures must be continued many months.

Almost no results have been achieved by the internal and subcutaneous administration of organotherapeutic remedies (thyroid, lymph-gland, and marrow preparations). Whait announced some success after bone-marrow tablets, but no lasting cure. The diagnosis of other cases described as successful (Macalister) is not sufficiently certain.

All in all, therefore, we are simply thrown back on the symptomatic

PSEUDOLEUKEMIA.

SYMPTOMS AND COURSE.

treatment, which has been found to mitigate the sufferings of the patient and keep up strength as long as possible. Among the measures which have achieved at least temporary success in the alleviation of symptoms may be mentioned inhalations of oxygen and of carbonic acid (Ewart). Among the remedies employed to excite the appetite, Litten and Vehsemeyer especially recommended berberinum (the hydrochlorate of which is soluble with difficulty, the sulphate and phosphate readily soluble). This has been now and then recommended as a remedy for malaria and also as a styptic. Its dose is from 0.1 to 0.3 gm. several times daily, in pills, in solution or subcutaneously.

Under the name *pseudoleukemia* (Cohnheim) is included a large number of cases showing the common symptom of enlargement of the lymphatic apparatus, especially the lymph glands and the spleen, just as in lymphatic leukemia. They are, nevertheless, differentiated from the latter by the blood-picture, which manifests a diminution in the red blood-corpuscles, but no particular increase of the whites.

From the early literature the cases of Hodgkin and Wunderlich are

especially identified with this disease, and it is, therefore, frequently designated in honor of the first describer as *Hodgkin's disease.* The names *lymphosarcoma* (Virchow, Langhans) and *malignant lymphoma* are likewise frequently employed as synonyms.

We have seen previously that the blood-picture in these cases, so frequently designated as normal or as merely anemic, still shows certain peculiarities which closely ally it to lymphatic leukemia. In other words, on a careful investigation of the blood-histology, even when the proportion of W. : R. is normal, or the whites are only moderately increased, we always find a *relative increase in lymphocytes.* In contrast to true leukemia the original anatomic conception of pseudoleukemia has gradually broadened with its clinical diagnosis. Leukemia, too, was first recognized in the cadaver (Virchow), and only later, after Virchow's masterly description had risen to the dignity of a classic, was the diagnosis made during life. Yet in true leukemia this was easy and natural, while in pseudoleukemia the adaptation of pathologic knowledge to clinical cases often left wide gaps, and consequently the clinical conception of pseudoleukemia eventually came to be only a collective name for all possible generalized lymphomatoses which manifested no leukemic blood-picture.

From this heterogeneous mass we have gradually succeeded in creating a somewhat clearer picture by the separation of certain clinical forms which have become more evident in the course of time.

In a large number of pseudoleukemia-like cases, the blood of which did not show the relative lymphocytosis described as characteristic, but an actual normal or only anemic condition, there is good reason for believing that we have to do with an entirely different disease—namely, either a special form of *glandular tuberculosis* or the affection described by Kundrat, from Virchow's series of lymphosarcomata, under the name lymphosarcomatosis.

In order to distinguish between these and even other similar diseases, it is no longer justifiable to accept the criterion which prevailed a short time ago—namely, a leukemia-like appearance without the leukemic blood-picture. In the discussion of the diagnosis we will show what requirements are necessary in order to pronounce a case pseudoleukemia.

The symptoms of pseudoleukemia are often so exactly like those which we have described for chronic lymphatic leukemia that a detailed description of them would be for the greater part a repetition. We intend to give, therefore, only a summary of the points wherein they

differ. Nevertheless, we must first insist that the value of certain differences is difficult to estimate, because the conception of pseudoleukemia is not everywhere comprehended within our sharp limits, so much so in fact that in the old cases we often have no criterion for determining with certainty the pseudoleukemic nature of a disease.

The disease begins insidiously with a **swelling of the lymphatic structures,** in which no previous alteration was noticeable or in which a longer or shorter time before a hyperplastic condition existed as a result of another affection (see Etiology). The marked predisposition of the male sex which we remarked in all the other lymphemic diseases, especially acute leukemia and chloroma, but even in chronic lymphatic leukemia, though not so evidently, is found also in pseudoleukemia (Brousse and Gérardin, Gowers). According to Rudler, the male sex is three times more frequently affected than the female. The age of predilection lies between twenty and forty, though the disease is not extremely rare later. Even among children a considerable number of cases are known (Fischer, 7 among 12 patients). The largest lymphomata are most commonly found in the cervical region.

We distinguish two varieties of tumors, soft and hard.

The *soft* form simulates in every particular the lymphomata of chronic lymphatic leukemia. The tumors vary from soft to elastic, they are sharply defined from one another, elliptic in shape, and have a smooth surface. These glands may in the course of time change to hard, and both forms frequently exist side by side in the same patient. Moreover, a decision as to consistence is at times difficult.

Again, the lymphomata are often *hard* from the beginning. An exact percentage can not at present be stated, even with the large number of statistics at our command, because in this group of hard lymphomata are gathered all the diagnostically uncertain forms, and even some that evidently belong elsewhere (tuberculosis, lymphosarcomatosis), so that the pseudoleukemic picture is obscured.

The **spleen** is usually, though, as in lymphatic leukemia, not constantly, enlarged. Nevertheless, it is in the hard form of pseudoleukemia that the largest spleens on record have been observed. In the rare cases in which the external glands are not enlarged, the splenic tumor may constitute the most conspicuous symptom. Yet here, as in the glandular tumors, the differentiation of the different varieties may be impossible. Moreover, we have not a sufficiently large number of carefully investigated cases to decide whether isolated enlargement of the spleen can justify the diagnosis of pseudoleukemia, or whether, as Türck suggests, we have to do with a lymphosarcomatosis in Kun-

PLATE IV.

Pseudoleukemia, Showing Masses in Neck with Edema of Face (Longcope).

drat's sense. Rare cases of isolated splenic tumor with a relative lymphocytosis (usually following malaria) which ran an unfavorable course support the view that we may have a pseudoleukemia with a predominant or even exclusive localization of the lymphatic overgrowth in the spleen.

The lymphatic hyperplasia of the **bone-marrow** seems to be less constant than in true lymphatic leukemia, and in any case it produces even fewer clinical symptoms. Several cases described under the names myelogenous pseudoleukemia (v. Baumgarten), lymphadenia ossium (Nothnagel), in which the principal alterations were found in the bone-marrow, will be discussed with the so-called multiple myelomata in the section on Diagnosis. Since the blood-picture peculiar to them is only one of anemia and shows no increase in lymphocytes, these cases may be separated from the actual pseudoleukemias.

The **blood-picture** may be considered the chief characteristic of pseudoleukemia, as of leukemia. As detailed in the introduction, a considerable alteration in the number of leukocytes has been found in numerous cases of pseudoleukemia. Indeed, this observation was made by Cohnheim in the first case described as pseudoleukemia. The assertion that the corpuscular constituents of the blood undergo no alteration in pseudoleukemia, apart from a moderate or severe oligocythemia and other signs of anemia, is not justified. In the cases attended with augmentation of the leukocytes, the increase in the blood-cells affects *exclusively the lymphocytes.* The increase in the entire number of white cells is often so slight that their proportion to the red blood-corpuscles is little, if at all, disturbed, a fact which is made more striking by the decided diminution in number of the other leukocytes, especially the polynuclear neutrophiles. Consequently, since the number of white blood-corpuscles is subject to marked physiologic fluctuations, no significance can be attributed to the absolute increase. The deviation from the normal is, as a matter of fact, recognizable only by study of the proportions of the different varieties of leukocytes. If we find 4000 lymphocytes to the cubic millimeter, this does not exceed the physiologic limits (33 per cent.) of a total number of leukocytes amounting to 10,000, which can not be considered abnormal; yet if the total number amounts to only 6000, which also lies within the physiologic limits, the percentage of lymphocytes is increased to 60 per cent., or about double the normal.

[This statement can not be accepted without question. In Cabot's series[1] of 32 cases in which differential counts are recorded 11 showed distinct lymphocytosis, while the remaining 21 gave normal counts or

[1] *Clin. Exam. of the Blood,* 5th ed., p. 177.

decided polymorphonuclear leukocytosis, with reduction in the number of lymphocytes. In Da Costa's series[1] of 10 cases lymphocytosis (combining the counts of large and small lymphocytes) was present in but 3, and the author states that the condition is rare. In Longcope's series[2] of 8 cases only 1 showed lymphocytosis. Numerous other statistics might be quoted to the same effect, and the editor's experience coincides with that of the authors quoted.—ED.]

This relative increase in lymphocytes has frequently been unnoticed up to the most recent times, and so in a large number of cases the most important clinical criterion of this disease is wanting. In the small number (in comparison with the immense number of so-called pseudoleukemia cases) of completely unobjectionable observations—that is, observations which were clinically and anatomically studied with thoroughness, this relative lymphocytosis has always been found. Moreover, a number of cases pronounced clinically and sometimes even at the autopsy to be pseudoleukemia, in which no blood-change was observed, have been later proved to be some other disease, and not infrequently a peculiar form of tuberculosis.

As to the time when this lymphocytosis originates we have no definite information. The fact that pseudoleukemia arises from lymphomata which began from a different etiology supports the assumption that the blood-alteration occurs only after the lymphomata have existed some time—in other words, some of the multiple lymphomata without blood-alteration possibly represent the advance stage of pseudoleukemia. Still, such a diagnosis is possible only *post hoc*, and the development of pseudoleukemia with a typic lymphocytosis from such lymphomata with a normal blood-picture by no means justifies the diagnosis of pseudoleukemia in concrete cases during the stage of generalized lymphoma without other symptoms. As a matter of fact, this stage is to be considered rather the cause than a forerunner, as we shall see when speaking of the affections of other organs (tonsils, skin).

The slightly lymphatic blood-picture frequently remains unaltered for a long time; in fact, death usually overtakes the patient before the general leukocytic count is markedly increased. Yet a rapid increase in white blood-corpuscles sometimes takes place a short time before death, simultaneously with a rapid advance of the other symptoms, just as we have seen in several cases of acute leukemia, *sub finem vitæ*. These cases constitute the basis of the frequently expressed view that pseudoleukemia is an aleukemic advance stage of lymphatic leukemia. A gradual transition into a lymphatic leukemia of long duration has so far

[1] *Clin. Hemat.*, p. 268. [2] *Bull. of the Ayer Clin. Lab. of the Penna. Hosp.*, No. 1, 1903.

PLATE V.

PSEUDOLEUKEMIA (Longcope).

been reported but rarely (Askanazy—two and a half years before pseudoleukemia, for the last one and a half years lymphatic leukemia of high grade at every examination of the blood; cases of lymphodermia perniciosa).

The localization of the pseudoleukemic process in the **internal organs**, together with the symptoms resulting therefrom, agree exactly with the conditions in genuine lymphatic leukemia. Still, certain processes, as, for instance, the urticarial affections, may be more common than in lymphatic leukemia. The lymphatic tumors of the skin are exactly similar (even Pfeiffer's case, in which attention was called to the rare localization of the lymphomata in the mammary region, is identical with a leukemic case described by Malherbe and Monnier). Moreover, the primary stages of lymphodermia perniciosa (Kaposi), the érythrodermie mycosique of French writers, which ordinarily runs the course of a marked lymphatic leukemia, are not rarely associated with only a relative lymphocytosis such as is characteristic of pseudoleukemia. These universal erythrodermias, in which not the slightest blood-alteration is noticeable in the primary stages, constitute to a certain extent alymphemic advance stages of pseudoleukemia, and to this extent represent analogues of the multiple lymphomata without blood alteration. A pseudoleukemia may develop from either. Yet, just as every generalized lymphomatosis is not necessarily identical with pseudoleukemia, or about to become pseudoleukemia, so little reliance can be placed on the transition of a general erythrodermia without lymphemia into pseudoleukemia (that is, lymphodermia perniciosa). The basic disease may be quite different (universal psoriasis, universal lichen ruber, medicamentous exanthemata of various kinds), and may have absolutely no relationship to pseudoleukemia, even though it manifests similar prodromal symptoms. Whether the whole course of this affection of the skin from its urticarial or eczema-like beginning to leukemia and tumor formation is to be considered an increase in intensity of one disease, or whether the pseudoleukemia which later becomes true leukemia is accidentally superadded as a complication to a universal dermatitis of long standing, is a question that our present knowledge is unable to decide.

The **course** of pseudoleukemia is usually slow and manifests no paroxysmal exacerbations. The glands often remain the same size for months and years at a time, occasionally becoming smaller, sometimes as a result of therapy, again spontaneously. The blood-picture shows but slight variations; as a rule, the proportion does not pass the boundaries previously set down for it—namely, W. : R. = 1 : 200 to

1 : 100, and occasionally it improves somewhat. Still, sometimes we see a sudden (Trousseau) universal enlargement of the lymph glands (the enlargement up to this time being confined to the cervical region) exactly similar to that observed in lymphatic leukemia.

Fever is not a frequent symptom of pseudoleukemia. More attention will be devoted to the peculiar pseudoleukemia-like affection described as chronic relapsing fever in the discussion of the diagnosis.

The manner of *death* is exactly similar to that described in lymphatic leukemia. It is the result either of intercurrent disease before the pseudoleukemia itself has become threatening, or (and, in fact, more frequently than in leukemia) of obstruction to respiration by the immense tumors about the air passages. When life is not prematurely terminated by these means, the disease itself progresses to death by a slow cachexia or otherwise almost without exception by transition into an *acute leukemia.*

Nevertheless, in this form of lymphomatosis the prognosis is not so absolutely hopeless as in leukemia. In a certain number of cases, by energetic treatment with arsenic, we are able to bring the disease to a standstill or even sometimes to a long-continued improvement. Yet, whether a genuine, fully developed pseudoleukemia can be completely cured, is a question that can not at present be decided with certainty.

PATHOLOGIC ANATOMY.

The postmortem appearance of soft pseudoleukemic lymphomata simulates exactly that described for lymphatic leukemia. While in this soft form we see only a general hyperplasia of the parenchyma, in the *hard* form we find a structure in which the increase of the connective-tissue stroma is conspicuous. As we shall learn later in the discussion of the diagnosis, the sharp distinction of this form from similar clinical processes (especially tuberculosis) has become, to a certain extent, confused during recent years because cases from the older literature, which furnish the chief contingent for the study of the pathologic anatomy, have not been submitted to the criterions demanded by the present time.

These glands are also round or oval, flattened against one another, hard and incompressible to the finger, and often cut with difficulty or even grate under the knife. Their cut surface is grayish white to yellow, dry, does not well up, and is often uniformly fibrous or is crossed by whitish-yellow, thick bands.

The **spleen** is frequently characterized by an extraordinary size scarcely ever seen in true lymphatic leukemia. It is enlarged in all its

PLATE VI.

PSEUDOLEUKEMIA (Longcope).

diameters, and so appears like a giant spleen of normal shape. These pseudoleukemic spleens exactly resemble the lymphatic leukemic in structure. They are hard, usually riddled with very hard, whitish (in mild grades translucent), round or oval nodules. These nodules, sometimes confluent, are penetrated by vessels and correspond to the enlarged follicles, between which remains of the brownish-red splenic pulp are seen in the shape of broad bands (Langhans).

The **bone-marrow** has not been studied as regularly as its importance demands. In cases where it was examined, it was frequently found altered in exactly the same way as in outspoken lymphatic leukemia. The peculiar bone conditions seen in multiple myelomata and its osteosclerotic varieties will be described with the other affections coming into consideration in the differential diagnosis, since we are not justified in considering any of these cases pseudoleukemia (as a variety localized in the bones) without further study.

The **histologic structure** of the pseudoleukemic lymphomata corresponds exactly with that of lymphatic leukemia. In extirpated glands (Goldmann, Fischer) the normal arrangement, with the proliferating center of large cells and the peripheral layer of small cells, is still retained just as Bizzozero described in leukemia. True, Neumann's accumulations of eosinophile cells have been observed by Goldmann, yet this finding is apparently not characteristic, since it is found also in other varieties of lymphomata (Fischer), and is by no means constant in pseudoleukemia.

The parenchyma of the hard form is likewise composed of lymphocytes, though we also find, as Langhans has pointed out, polynuclear cells with nuclei regularly distributed throughout the cell body. These cellular constituents are more or less prominent, depending on the amount of connective-tissue stroma. This develops into hard, fibrous bands which may compress the lymphatic tissue here and there to almost nothing. All transitions up to this sclerotic form are seen in the different cases, and sometimes even in glands of the same case.

[Dorothy Reed,[1] in a careful histologic study of the glandular lesions of Hodgkin's disease, found lesions that she regarded as of a perfectly definite nature. There was a primary hyperplasia of the lymphadenoid tissue with a proliferation of the endothelial cells, forming mononuclear and polynuclear giant cells, and later a marked thickening of the reticular tissue of the glands, in the form of coarse anastomosing bands of connective tissue. Abundance of eosinophile cells was a noteworthy feature. Very similar histologic lesions were found

[1] *Johns Hopkins Hosp. Rep.*, 1902, vol. x., p. 133.

by Simmons[1] and Longcope.[2] Longcope describes in the earlier stages hyperplasia of the lymphadenoid tissue, a massing in the sinuses of epithelioid cells, giant cells and eosinophilic leukocytes, and thickening of the reticulum. Later the normal structure of the gland is lost, and there is seen a reticulum, in the meshes of which are found large and small lymphocytes, plasma cells, polymorphonuclear leukocytes, large uninuclear and multinuclear giant cells, epithelioid cells, and eosinophile leukocytes. Occasionally, by their rapid division, the epithelial cells form islands of syncitium.—ED.]

When retrogressive changes are found in the pseudoleukemic tumors (especially in the lymph glands) the diagnosis at once becomes doubtful. In these cases a careful investigation should be made to determine whether it is not a tumor-like tuberculosis (Sternberg) or a combination with tuberculosis (Fischer).

ETIOLOGY.

In regard to the excitant of pseudoleukemia, our knowledge is no greater than in lymphatic leukemia. Often as the disease has been described as infectious, and often as micro-organisms have been found in it or tumors produced by the injection of pieces of the lymphomata into animals (Roux and Lannois, Delbet), we have as yet no convincing proof, though the probability is great, that the positive inoculation experiments represented cases of tuberculosis.[3]

Since Trousseau's time, local affections of lymphatic structures, especially about the head (for instance, enlargements and abscesses of the tonsils), have been considered as forerunners of the disease on account of the fact that the operative treatment (extirpation of the tonsils and glands by the knife) is not rarely followed by a sudden eruption of lymphomata over the whole body.

Among other forerunners a large number of infectious diseases are mentioned—for instance, malaria (frequent), typhoid fever, syphilis (Peter), measles, and scarlet fever; also the sting of a bee (Billroth). The occurrence in families observed by Casati (ten-year-old girl, father and grandmother), Biermer (2 sisters, age from three to four years),

[1] *Jour. of Med. Research*, 1903, p. 378.

[2] *Bull. of the Ayer Clin. Lab. of the Penna. Hosp.*, No. 1, Oct., 1903.

[3] Delbet raises this assumption to the level of a certainty when he says (quoted from Rudler): "Clinically we have to determine the nature of a disease the symptom-complex of which is defined. When we find cases, therefore, in which all the characteristic symptoms are present (generalized enlargement of the glands, leukocytosis, its peculiar cachexia), we are forced to the diagnosis of lymphadenoma. Further, when bacteriological examination and animal experimentation show that the case is tuberculosis, we must logically conclude that certain cases of lymphadenoma are of a tubercular nature."

PLATE VII.

CERVICAL, SUBMENTAL, MEDIASTINAL, BRONCHIAL, RETROPERITONEAL, AND LEFT AXILLARY TUMORS FROM CASE SHOWN IN PLATE V.

The tongue is visible at the top of the picture in the middle line. A short distance below is the thyroid gland. The axillary tumors are attached to the mass of cervical glands on the left side (Longcope).

Among the cases of lymphatic tumors from the earlier literature a number have already been noted which show more than a simple accumulation of lymphatic cells, inasmuch as we find, in addition, retrogressive changes (caseation and other necroses) or heterogeneous cell varieties—namely, polynuclear cells and typic Langhans' giant cells. It was in reference to these cases that Wunderlich, and later Billroth, suggested the idea of scrofula.

Moreover, in the course of the last ten years cases have been described in which animal experimentation or histologic and bacteriologic investigation have been able to demonstrate tuberculous changes in the enlarged lymphatic structures. This demonstration has stood the test of the most careful scrutiny, and we are now in a position to assert positively that a large number of cases of pronounced malignant lymphoma, both clinically and at autopsy, were not only associated with tuberculosis (Fischer), but represented pure tuberculous disease. This tuberculosis of the lymph glands, which may lead to confusion with pseudoleukemia, shows certain peculiarities. The typic structure of the tubercle is lacking. The accumulations of large endothelioid cells are more diffuse and show between them only occasional tubercle bacilli. Later in its development we may find widespread caseation, and, at the margin, giant cells and tubercle bacilli in large numbers. In addition to this "large-cell tubercular hyperplasia" (Ziegler), we sometimes find quite large amounts of pure hyperplastic lymphatic tissue. Much more rarely we see a collection of epithelioid cells resembling the ordinary typic tubercle with a lymphocytic wall, and a central caseated area containing giant cells.

The question whether we have to do with tuberculosis in all these cases will be decided only after a considerable increase in our present material. The fact that the more careful and accurate our technic becomes, the more frequently is the tubercular nature demonstrated by the finding of bacilli, and by animal experimentation speaks decidedly in favor of the extraordinary frequency of tuberculosis. Yet the question whether we have to do with a pure tuberculosis (as Sternberg believes he has demonstrated) or with a mixture of tuberculosis with some form of neoplasm (sarcoma, Ricker) is much more difficult. On account of the small amount of material at command we are not yet in a position to decide the first part of the question—namely, whether we are dealing with tuberculosis alone. Other and more extensive investigations must first be undertaken along the lines indicated by Sternberg.

PLATE VIII.

SECTION THROUGH LYMPH-GLAND OF CASE SHOWN IN PLATE VI.

Showing uninuclear and multinuclear giant cells, various forms of epithelioid cells, and moderate numbers of eosinophilic leukocytes (Longcope).

PLATE IX.

SECTION FROM A LYMPH-GLAND IN PSEUDOLEUKEMIA.

Showing thickened reticular network enclosing lymphoid cells, plasma cells, epithelioid cells, and giant cells (Longcope).

The differentiation of the other symptom-complexes mentioned above may be even more difficult, since we have not the etiologic factors evident in tuberculosis to aid us.

1. **Anæmia pseudoleukæmica infantium** (v. Jaksch), anæmia splenica of English writers, or pseudopernicious anemia of children (Ehrlich). This consists of a high-grade anemia characterized by a blood-picture recalling somewhat pernicious anemia. We find, for instance, nucleated red blood-corpuscles (megaloblasts and normoblasts), a diminution in the number of erythrocytes, frequently a marked increase in leukocytes, and the appearance of myelocytes (Ehrlich, Engel; the blood-picture of the case reported by Bloch and Hirschfeld [see p. 555] as leukemia resembles exactly anæmia pseudoleukæmica infantium). Unfortunately, accurate descriptions of the blood-finding are wanting in most of the reports (Symes, Hochsinger—Reports on the Anemias of Children, by Fischl and Siegert; Henoch will allow no differentiation to be based on the blood-finding, which he considers as a "Wechsel auf die Zukunft"), and we are consequently thrown back on the other clinical symptoms for the definition of the disease. The disease affects especially young children between the ages of nine months and two years. It terminates either in death or, after lasting months, in recovery. Its most conspicuous characteristic is a hard (sometimes very hard), smooth swelling of the spleen, which is often visible through the emaciated abdominal wall, and to which Battersby called attention as far back as 1849. The liver is—in contrast to the very great enlargement almost regularly seen in the leukemias of very young children—not very much enlarged, and retains its sharp inferior margin (v. Jaksch). The anemia is evidenced by the pallor and puffiness of the skin, which frequently shows, especially on the face, a diffuse sulphur yellow or sometimes a more circumscribed yellow tone (Symes), diminution of the red and often marked increase of the white blood-corpuscles. In addition we find hemorrhages into the skin, and the mucous membrane of the nose, mouth, and intestine.

Further investigations are necessary to show whether this blood-picture (with megaloblasts and myelocytes) is a constant feature; for if it is, the differentiation from outspoken cases of lymphatic leukemia would become relatively easy. The remaining clinical symptoms are not sufficiently definite for a differential diagnosis from leukemia or a series of other anemic conditions of children. High-grade leukocytoses, such as may occur in this affection, have apparently not the same significance in children as in adults (v. Jaksch). Moreover, a predominance of the lymphocytes is to be considered the rule, even normally

PLATE X.

Section from a Lymph-gland in Pseudoleukemia.

Stained with Mallory connective-tissue stain (Longcope).

PLATE XI.

SECTION FROM A LYMPH-GLAND OF CASE SHOWN IN PLATE V.

Showing large islands of almost undifferentiated protoplasm containing nuclei of the giant-cell type. Too somewhat isolated cells are undergoing mitosis. Surrounding the islands are seen lymphoid cells, plasma cells, epithelioid cells, giant cells, and eosinophilic leukocytes lying in a network of reticulum (Longcope).

PLATE XII.

Karn M. Hall, fec.

SECTION THROUGH SPLEEN IN CASE OF PSEUDOLEUKEMIA.

A lymphomatous nodule is extending through the wall of a large blood-vessel and partially occludes the lumen (Longcope).

(Loos, Engel). Bearing in mind these uncertainties, we must realize that only those cases which have been subjected to our modern methods can give anything like positive evidence in regard to the relation of this disease to leukemia.

The frequent occurrence in syphilitic children gives rise to special difficulties. In these cases the basic disease may produce quite similar symptoms (diffuse hereditary syphilitic infiltration of the skin [Hochsinger], marked enlargement of the spleen, moderate tumor of the liver, high-grade anemia) to both anæmia pseudoleukæmica infantium and true leukemia. The same may be said of the pathologico-anatomic finding (round-cell infiltration of the parenchymatous organs) and of the blood-picture (nucleated red blood-corpuscles [Loos], lymphocytosis [Engel]). Moreover, specific therapy aids little in the diagnosis, since, on the one hand, mercury and iodids do not always cure, and, on the other, the disease not rarely terminates favorably without specific treatment.

A larger number of cases, carefully examined according to the demands of modern diagnosis and compared with the normal conditions, is likewise necessary to make this subject clear.

2. **Splenic Anemia** (Strümpell).—On account of our defective knowledge of the normal conditions, and on account of the small amount of available material, the relations of the disease described by Strümpell as splenic anemia to pseudoleukemia and lymphatic leukemia are even less definite than those of anæmia pseudoleukæmica infantium. The rarity of the disease leaves us with insufficient material on which to form a judgment of the nature of the disease. It is sometimes reckoned with the severe essential anemias, again, with lienal pseudoleukemia. It is characterized, in addition to the symptoms produced by enlargement of the spleen, by a high-grade anemia, expressed by an oligochromemia and oligocythemia, which are sometimes associated with a mild leukocytosis. The not rare paroxysmal course (somewhat like that of pernicious anemia) is particularly noticeable, the most marked anemia and enlargement of the spleen alternating with evident and long-lasting remissions. Moreover, we must contest the designation lienal pseudoleukemia for the same reasons that we offered against the designation lienal leukemia. We should not name the leukemia from the organs showing the greatest change, but from the kind of change, and we should proceed in the same way in the naming of the varieties of pseudoleukemia. Though certain cases of this anemia are found associated with an increase in lymphocytes, we have no case associated with the occurrence of myelocytes; consequently, as the cases of generalized lymphomatosis with lymphocytosis are placed in close relation

to lymphatic leukemia, so these cases of splenic anemia with lymphocytosis should occupy the same position.

[The contributions to the pathology of "splenic anemia" that have recently appeared[1] do not support the old view that this condition is a form of splenic pseudoleukemia. It is questionable whether the conditions designated by the term splenic anemia all belong to a single class. There is some evidence to show that different pathologic processes have superficial resemblances that makes their clinical differentiation difficult or impossible. At any rate there is not at the present time much evidence to justify the classification of the condition with pseudoleukemia. Many of the recorded cases have shown normal or practically normal conditions of the blood.—Ed.]

3. **Chronic Relapsing Fever** (Ebstein).—Under this name a disease was described which runs a course exactly like that reported first by Pel (though previously recognized by others—Gowers, Murchison) as a special form of pseudoleukemia. Its characteristic is a regular alternation of pyretic and apyretic periods, which last from one to three weeks or sometimes less. A splenic tumor becomes at the same time clinically perceptible, which frequently increases and decreases with the paroxysms and remissions. More rarely we find lymphomata and other localized sarcoma-like round-cell tumors. The anatomic picture frequently suggests lymphosarcoma or Hodgkin's disease, consisting, as it does, of a malignant tumor (Hammer suggests sarcoma, but compare what is said about this case under multiple myelomata) situated in some one or other lymphoid organ (glands, spleen, bone-marrow). The diagnosis of these cases is made more difficult by the occurrence of very similar symptoms in severe malaria (van der Scheer) which terminates in recovery; though quinin—usually effective—fails, and arsenic alone proves successful, exactly as in pseudoleukemia. A similar recurring fever has been sometimes observed in other malignant tumors (Hampeln, Kast), and is to be attributed to their irregular growth. Further, even in the cases reckoned as pseudoleukemia, the finding is not always a pure lymphadenoid one (spindle- and epithelioid-cell tumors, Schottelius in Völcker's case), and this, in connection with the combination (even though possibly accidental) of a previously existing skin tuberculosis (Hanser), supports the idea expressed by Sternberg, and before him by Askanazy, that we often have to do in these cases with the peculiar tubercular lymphomata which simulate pseudoleukemia. The explanation of the disease picture, in short, as a modification of pseudoleukemia, can scarcely, therefore, be considered complete. Whether

[1] Sippey, Osler, Rolleston, Brill, F. Taylor, Stengel.

cases of pseudoleukemia with intermittent fever are to be regarded as a special class must be left to future investigation. So far, neither the pathologic anatomy nor the blood histology is sufficiently understood to decide the proper classification of these cases.

4. **Lymphosarcomatosis.**—Recognized among the first of the lymphatic processes—though sharply defined only later by Kundrat, who associated it with pseudoleukemia—this affection may prove exceedingly difficult of diagnosis. The name lymphosarcoma is used in its old signification, somewhat modified and narrowed. Like the forms of generalized lymphomata, the disease takes its origin from the lymphatic organs, from the proliferating tissue of the lymph glands, the follicles of the spleen or other preformed collection of lymphocytes; and, like all lymphatic tumors, especially in the region of the head, from the mucous membrane of the throat, the tonsils, and the skin glands. The greater number of these lymphosarcomata sensu strictiori can never be confused with pseudoleukemic tumors, since they occur as circumscribed masses, showing early ulceration, especially on the mucous membrane of the mouth and upper air passages (Störk), while pseudoleukemic, like lymphatic leukemic, tumors, never show a primary breaking down.

Still we often meet serious difficulties in the frequent cases in which the tumors take their origin in the lymph glands (especially of the neck), and in the rarer cases in which the spleen alone seems affected, and increases occasionally to extraordinary dimensions (Türck). Nevertheless, the similar course of the latter to a malignant tumor makes an evident difference between it and pseudoleukemia.

We have learned to recognize pseudoleukemia and lymphatic leukemia as generalized lymphomatoses, in which the tumors remain localized in capsulated organs (especially lymph glands), after the fashion of a benign tumor, never pass over these prescribed boundaries, and in their growth only force to one side and compress the neighboring tissue without destroying it. Moreover, their manner of distribution is not like the dissemination or metastasis of malignant tumors; on the contrary, these lymphomata are hyperplasias of the tissue normally present at the site where, speaking generally, the specific irritation arose. In contrast to this lymphosarcoma is a local process which, after the fashion of a malignant tumor, is capable of breaking through everything in its immediate neighborhood, and spreading from its primary location throughout the body by means of the lymph vessels. Since this dissemination proceeds gradually from one group of glands to another, and since the primary tumor is absolutely localized to lymphatic structures

(glands, lymph follicles, or other accumulations of lymphadenoid tissue), we find multiple lymphatic tumors, as in leukemia and pseudoleukemia. Moreover, since the oldest foci are not necessarily the largest, we may find large tumors far distant from the primary focus and only connected with it by an unbroken chain of very small ones. Still, the secondary tumors are usually distributed in a gradually decreasing size from the primary ones, so that those farthest away are also the smallest (Kundrat).

When the malignancy of the process is shown by the non-confinement of growth, the diagnosis between lymphosarcoma and leukemia or pseudoleukemia is even clinically easy. But so long as the lymph gland tumors do not break through their capsule and invade the surrounding tissue, the differentiation from pseudoleukemia and leukemia is clinically impossible. True, sometimes the simultaneous occurrence of a lymphosarcoma in the neighboring mucous membrane (particularly of the throat) permits a positive diagnosis. Yet, in general, we must base our decision on the blood-finding, which in leukemia and pseudoleukemia, shows an increase in lymphocytes; in lymphosarcoma, either a normal count or even a decrease (sometimes extreme) in lymphocytes (Reinbach, Türck, see this Vol., p. 82).

Therefore, a positive diagnosis as to whether we are dealing with leukemia or not can be made only from the blood-finding. Yet, with an absence of the characteristic lymphocytosis, the anatomic examination of the tumor itself is alone sufficient to tell whether the case is one of lymphosarcoma or some other form of lymphoma, particularly the peculiar tuberculous form previously described.

The study of the histology of the blood will fail us in only one case, namely: when a lymphosarcoma is grafted on an already existing lymphomatosis (usually a pseudoleukemia with the proportion of reds to whites unaltered), a combination which is not rarely observed and which leads to the view of a genetic relationship between the two, somewhat similar to that presupposed in the origin of a malignant tumor from a benign one (Türck). In this case, when the clinical picture is deficient, the microscopic examination of the affected organ alone is capable of leading to a diagnosis. While in pseudoleukemic lymphomata the capsule is always respected and other adenoid nodules are developed not by metastases from this lymph-cell accumulation, but from cells originally in loco; the nodules of lymphosarcomatosis grow unchecked beyond the natural boundaries, breaking through the capsule at different places. True, within the individual lymphatic organs in leukemia and pseudoleukemia, we frequently find a confusion of the different parts normally separated from one another (the cortical nodules and medullary bands

of the lymph glands, the lymph follicles in the spleen and in the mucous membranes) on account of the fact that they are not strictly held apart by connective-tissue walls and slight disturbances readily lead to their confluence. In this case the arrangement of the elements and the shape of the cells must act as the criterion. In pseudoleukemia we find only the simple structure described under the pathologic anatomy, in other words, the adenoid tissue consists of a more or less rich uniformly arranged connective-tissue reticulum, in which are deposited the round cells corresponding to the small lymphocytes. The tumors of lymphosarcomatosis, on the contrary, are (according to Kundrat) characterized by an irregular arrangement of the stroma and a smaller number of larger-sized cells.

[Türk [1] discusses the lymphomatoses dividing them into three groups. The chronic benign form and an acute and a chronic malignant form. The first two groups he subdivides into alymphemic, the sublymphemic, and the lymphemic. The sublymphemic chronic benign forms he identifies with Pinkus' pseudolymphemia. The chronic malignant form corresponds with lymphosarcomatosis which may be local or generalized. He notes that transitional cases join the different groups with each other. He holds that chloroma is an acute lymphomatosis with a green color of the lymphoid proliferations, and a special tendency to involve the periosteum and marrow. He does not regard the green coloration as warranting special classification. The involvement of the periosteum, dura, and serous membranes indicates a moderate malignancy which is confirmed by the discovery of the characteristics of acute leukemia in the blood-making organs. The point he aims at establishing is that in situations where the conditions do not favor the washing away of the cells, there is evidence of local injury, and when the cells are produced in great number in the lymphatic system there is local accumulation with formation of tumor masses. The local accumulations are more likely to occur in aleukemic forms. Pappenheim, in discussing the nature of leukemia [2] and the occurrence of lymphemia without enlargement of the glands, expresses the view that there is no sharp dividing line between pseudoleukemia and lymphatic leukemia. When the process is confined to the glands and spleen, the clinical picture is that of Hodgkin's disease, but when the bone-marrow is involved the blood at once presents the character of lymphemia.—ED.]

Multiple Myeloma.—We still have left the differential diagnosis of the disease known as *multiple myelomata*, the relationship of which to lymphatic conditions appears very close. It is characterized by a

[1] *Wiener klin. Woch.*, 1903, No. 39. [2] *Zeitschr. f. klin. Med.*, 1900, p. 171.

typical syndrome which makes its diagnosis very probable, even during life. The disease is introduced by indefinite feelings which later develop to lively pains, especially in the rump, breast, back, neck, and more rarely in the limbs, associated with spontaneous pain or tenderness on pressure in the bones of these parts (spinal column, ribs). Still later visible changes often occur in the bones (swellings, spontaneous fractures, particularly in the ribs and sternum), and others are indicated by the bending forward of the head and kyphotic lowering of the vertebral column. At the same time a severe anemia develops, accompanied by various nervous disturbances, as neuralgia, motor, and sensory paralyses of the cerebral nerves (hypoglossal, facial, Senator). An additional characteristic is the excretion of the so-called Bence-Jones' albumose in the urine, which we previously mentioned as an exceptional occurrence in lymphatic leukemia (p. 593). The anatomic finding consists of peculiar lymphoma-like tumors in the bone-marrow, which usually terminate in softening (this is the reason for the fractures), and in the early cases gave rise to the idea of osteomalacia. Less frequently [1] the process terminates, not in softening, but in an osteosclerosis of the compact bone which leads to a disappearance of the medullary spaces, so that only a very small remnant filled with a red tissue made up mostly of lymphocytes is left. The blood shows an anemia, but no increase in white cells, and, in the carefully reported cases, no relative lymphocytosis. Lymphomata are not rarely found in the internal organs.

The localized lymphoma formation, usually seen in multiple myelomata with its negative blood finding, stands in contrast to the diffuse lymphoid hyperplasia which, according to Neumann, constitutes the basis of every leukemia. Moreover, the transition of a localized into a diffuse lymphatic hyperplasia of the bone-marrow, as suggested by Pappenheim, has so far never been observed.

Unfortunately we have, from none of the cases so far, such an accurate record of the histologic examination that the diagnosis of the variety of round cells is entirely objectionless; for it is exactly in the bone-marrow that these cells are difficult to diagnose on account of ready confusion with others. The great similarity of the advance stages of true bone-marrow cells and of red blood-corpuscles with lymphocytes, may give the most different histologic processes quite similar appearances. In this regard, the finding of Charcot's crystals in Noth-

[1] We have mentioned Hammer's case in the section on Chronic Relapsing Fever, where we took the observer's explanation of the tumors as sarcomata. Yet, according to v. Baumgarten's explanation and the cases of v. Baumgarten (myelogenous pseudoleukemia) and Nothnagel (lymphadenia ossium), it appears more likely that it was a pseudoleukemic process.

nagel's well-known case of lymphadenia ossium becomes especially puzzling, since they occur in lymphatic tumors, at most, only exceptionally (see Chloroma, p. 579).

We are, therefore, not yet so far advanced as to be able to define the absolute relation of multiple myelomata or other forms of this affection to lymphatic pseudoleukemia. We can no more bring the cases with a normal blood-finding into this category than the cases of multiple lymphomata without lymphemia. It is possible that the experimental production of changes in the bone-marrow by the artificial induction of albumosuria (Zuelzer) may throw some light on the subject.

[In a review, under the title of "Myelopathic Albumosuria,[1]" S. J. Meltzer[2] refers to the history of this condition and literature up to the present time. In the recent paper of Simon[3] the subject was carefully reviewed. Later, F. Parkes Weber,[4] collected and analyzed the data in 28 reliable cases. To these Meltzer now adds 1 of Milroy,[5] 3 of Anders and Boston,[6] 1 of Boston alone,[7] and 1 of Vickery,[8] all of which, with his own case, make the total number of recorded instances 35. He believes that the number of cases does not adequately represent the frequency of the condition, since there are cases on record of multiple myeloma with albumin in the urine, while at the autopsy the kidneys were found normal, and, again, pathologic cases of multiple myeloma reported recently in which there have been no clinical notes. The fact that Weber, even in his second case, did not discover that the albumin in the urine was really albumose until after two months, and the fact that Jochmann and Schumm[9] have, as recently as 1901, described their typical case as one of osteomalacia, and only lately corrected this erroneous nomenclature, show that the disease is quite readily overlooked or erroneously classified. As far as diagnosis is concerned, Meltzer states that the coincidence of myeloma and albumosuria constitutes the essential feature of the disease.—ED.]

We must further mention the cases (referred to under Lymphatic Leukemia) of symmetrical lymphoma development in the lacrimal and salivary glands which Mikulicz believes to be a disease type. Their simple lymphomatous structure, their reaction to arsenic, and their clinical resemblance to true lymphemia cases bring them close to pseudoleukemia; the possibility of cure and the absolutely normal blood-

[1] *Kahler's Disease; Multiple Myeloma.* [2] *Med. Record*, June 18, 1904.
[3] *Amer. Jour. of the Med. Sci.*, 1902, p. 939. [4] *Amer. Jour. Med. Sci.*, 1903, p. 644.
[5] *Jour. of Path.*, vol. vii., p. 95. [6] *Lancet*, Jan. 10, 1903.
[7] *Amer. Jour. of Med. Sci.*, April, 1903.
[8] *Trans. of the Assoc. of Amer. Phys.*, 1902, vol. xvii., p. 171.
[9] *Münch. Med. Woch.*, 1901, p. 1340; *Zeitschr. f. klin. Med.*, 1902, vol. xlvi., p. 445.

picture permit their comparison with multiple lymphomata without lymphemia, which we sometimes find as the forerunner of a lymphemia.

If we consider now the ordinary large tubercular lymphomata and the malignant tumors of the lymph-glands, carcinoma metastases and sarcoma, we shall have recalled all the diseases occurring in the lymphatic apparatus.

The sharp differentiation which we have made between lymphemic and non-lymphemic conditions will, we are confident, act as the criterion of diagnosis between these different diseases in the future.

The differentiation between lymphatic leukemia and pseudoleukemia with their closely related lymphemia is less sharp. The cases with a moderate increase of lymphocytes are especially difficult; and, as we have remarked in the introduction, we are not infrequently forced to make the diagnosis more from the general impression created than from any definite clinical symptoms. In general, we are inclined to regard all cases showing a deterioration of the blood as lymphatic leukemia, and cases with a regular course lasting years, even when the ratio of W. : R. is 1 : 100, as pseudoleukemia.

What was said in the previous section (p. 625) applies also to the differentiation of pseudoleukemia from myeloid leukemia.

In conclusion, therefore, we divide the old broad conception of pseudoleukemia into three diseases:

1. True pseudoleukemia. In this class we place the generalized lymphomatoses with relative lymphocytosis, and comprehend them in one group with true lymphatic leukemia.

2. Lymphosarcomatosis, generalized lymphomatosis without blood alteration or with a decrease in lymphocytes and with characteristic malignant tumors.

3. Other not purely lymphatic diseases of the lymph apparatus, as tuberculosis and malignant tumors.

PROGNOSIS AND TREATMENT.

In regard to the prognosis and therapy we can only repeat what we said under lymphatic leukemia. Therapeutic results are more frequent than in lymphatic leukemia, especially under the energetic administration of arsenic; yet, even here a persistent effect is rare. Nevertheless, all the symptoms may be held in check for months and years even without an actual cure. We must repeat that lymphomata accompanied by an increase of lymphocytes in the blood provide a signal for the most guarded prognosis.

In regard to the cases of generalized lymphomatosis with no blood

alteration, which cannot, therefore, be regarded as pseudoleukemia, the prognosis is entirely dependent on their etiology. As mentioned previously, a certain percentage of these cases constitute an advance stage of pseudoleukemia, whether it is to be considered that the lymphemia sets in as a later development or the transition to pseudoleukemia comes on as a complication. These etiologically indefinite lymphomata are frequently tractable to therapy. When the enlarged glands are not too widely distributed and are extirpated, a remission frequently occurs which may last a long time or even forever; yet, in other cases, the extirpation seems to act as a factor inducing more rapid spread. Not rarely they disappear under the administration of preparations of iodin, and, as described in a previous section, they are especially favorably influenced by arsenic. This arsenic therapy must be continued for a long time and is often successful only by the alteration of internal, subcutaneous and intraglandular administration.

[The results obtained from *x*-ray treatment will be referred to under the treatment of Myeloid Leukemia.—Ed.]

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MYELOID LEUKEMIA

BY

DR. A. LAZARUS

MYELOID LEUKEMIA.

SINCE the theoretical questions in regard to the different forms of leukemia were thoroughly discussed on page 125, as well as in the introduction to the volume we will confine, ourselves in the following to the description of the purely clinical peculiarities of myeloid leukemia ("myelemia," "myelogenous seu medullary, seu bone-marrow celled leukemia").

This problem meets at once no small obstacle in an insufficient amount of material to render our observations complete. For, as has been shown in the above-mentioned sections, we can not, in the light of our present knowledge, consider merely a pathology and therapy of "leukemia." On the contrary, we realize that the two forms of leukemia, the lymphatic and the myeloid, are so distinctly separated from one another that a close relationship between them is not at all likely. Both diseases have, in fact, as much and as little in common, as, for instance, typhus abdominalis (typhoid fever) and typhus exanthematicus, two diseases which owe their somewhat similar names to the similarity of several of their most prominent symptoms and, therefore, must be sharply differentiated.

With this in view, we break from the line of procedure generally followed thus far, of considering the etiology and special symptomatology of both leukemias together. It is necessary, therefore, and we hope advantageous to the advancement of knowledge to base this chapter on cases which belong without doubt to one or the other form. We wish only to remark that in the material thus sifted, we must not overlook the question whether this differentiation of the two diseases discovers more clinical characteristics that are common or more that differ.

Unfortunately, by far the greater part of the data given in the literature fails to fulfil the necessary demands made by Neumann, thirty years ago, and is, therefore, useless for our purpose. True, a certain number of descriptions of the blood in leukemia have come down to us from the earlier times, even before the introduction of our present clinical methods, which are so accurate that we can decide the diagnosis of individual cases to-day. Nevertheless, considering the amount of

material, these cases are exceedingly few, and in contrast to these, the greater number of publications on leukemia, even during the last ten years are so defective as to be unavailable. We are constrained, too, to omit those cases which are designated as pure lienal, lieno-medullary or medullary, that is myelogenic when no accurate description of the microscopic blood-picture accompanies them.

The following description, therefore, is based on a comparatively small number of cases, and will possibly bring forward less actual material than monographs written ten years ago. Numerous assertions in regard to the etiology, pathologic anatomy, complications, etc., made by other manuals, and text-books can not be considered here, because it is uncertain whether they refer to lymphatic or myeloid leukemia.

ETIOLOGY.

Myeloid leukemia is a reasonably rare disease. Definite data can not at present be given, since in the statistical reports showing the frequency of leukemia a separation of the two forms has not been made. Judging from the cases in which the blood finding was carefully described, the author's impression is that lymphatic leukemia is somewhat more common than myeloid.

Of 38 cases characterized as myeloid by the blood examination, 12 were in females and 26 in males.

In regard to age they were divided as follows:

Age.	Females.	Males.
1–10	1	1
11–20	3	0
21–30	4	7
31–40	4	7
41–50	0	8
51–60	0	3

The marked participation of the virile age, as has been generally recognized in leukemia, is striking. Among the 38 cases, 30 were between the ages of twenty and fifty. Females are apparently much less frequently attacked than males.

In regard to occupation and social position, I could find nothing that might tend to show a predilection. What was said previously in the chapter on the etiology of leukemia, is based on conjecture, and this is especially true in regard to myeloid leukemia which manifests no relationship to other diseases, as, for example, sarcomatosis or tuberculosis. Moreover, all attempts to attribute the disease to unsanitary conditions, poor food, worry, overwork, etc., must be considered idle.

Nothing positive can be drawn from the literature in regard to local differences or geographic distribution. Still, the large number of cases (39) which fell into the hands of one observer, Cabot, in Boston, is striking.

For a time trauma was made to play a special rôle in the etiology of leukemia. Yet, such a connection can by no means be regarded as proved. Recalling the fact that in many of the cases of myeloid leukemia the diagnosis was made quite accidentally and only in an ad-

vanced stages of the disease, it is readily intelligible that not infrequently cases may be discovered through an examination of the blood made on account of a trauma. In an extensive monograph on the traumatic origin of internal disease, Stern disposed entirely of the so-called cases of traumatic leukemia and came to the conclusion that no such indisputable case has been observed, even though the possibility can not be denied that the function of the blood-making organs may be deranged with such a result by injury or shock.

Since the first domination of bacteriology in the study of the etiology of disease, numerous attempts have been made to show a vegetable or animal cause for leukemia. Yet, none of these attempts has led to anything like a satisfactory result, whether limited to the microscopic demonstration or the artificial cultivation of the excitant, or extended to the transference of the disease to animals by inoculation.

A full report of these futile investigations is presented by Löwit, in the publication in which he endeavors to prove that a certain protozoon variety "hæmamæba leukæmiæ magna" is the cause of myeloid leukemia, and another "hæmamæba leukæmiæ parva seu vivax" is the cause of lymphatic leukemia. Only a comparatively short time has elapsed since the appearance of Löwit's paper, yet its probability is seriously impaired by the contradiction already experienced. Löwit's protozoa have been considered as artifacts especially by Türk, Litten, and Michaelis, and the suspicion has even been aroused that they are the basophile granulations of the mast cells which, as we know, are a constant constituent of myelemic blood. Still, before this question can be settled with unqualified certainty, further investigations must be made.

Moreover, the clinical study of myeloid leukemia has so far produced only very uncertain evidence that we have to do with an infectious disease. True, two observations may be considered worthy of mention—namely, Cabot's, in which a nurse became affected with myeloid leukemia and died a short time after he had nursed a typic case of the disease, and Obrastzow's, in which the same occurred with lymphatic leukemia. Yet, it is impossible from these two cases, to draw the conclusion that they were the result of direct contagion.

SPECIAL SYMPTOMATOLOGY.

THE BLOOD.

We will here add to the detailed description of the *microscopic picture* given on page 128, a few particulars in order to show more clearly the extraordinary diversity and yet sharp definition of this disease. (Compare Plate XIII.).

In brief the classical characteristics of myeloid leukemia are :

1. The occurrence of very many *mononuclear neutrophile cells,* Ehrlich's myelocytes *κατ' 'ξσχην.* These are encountered in all variations of size, from somewhat smaller than the normal red blood-corpuscle, to two or three times this size. In the same way the protoplasmic granules vary in number from a few to a number filling almost the entire cell.

2. The occurrence of mononuclear eosinophile leukocytes corresponding in size and number of granules with the preceding. Occasionally we meet very large examples three to four times the size of a red blood-corpuscle.

3. An absolute increase in the polynuclear neutrophile and eosinophile cells.

4. An absolute and usually also a percentage increase in the mast cells.

5. Atypic forms of white blood-corpuscles (compare p. 132), especially forms showing mitoses.

6. Nucleated red blood-corpuscles, more frequently normoblasts, less frequently megaloblasts.

We intend to elucidate this brief review of the morphologic changes (a more complete description of which has been given in another section) by a few figures from our own studies.

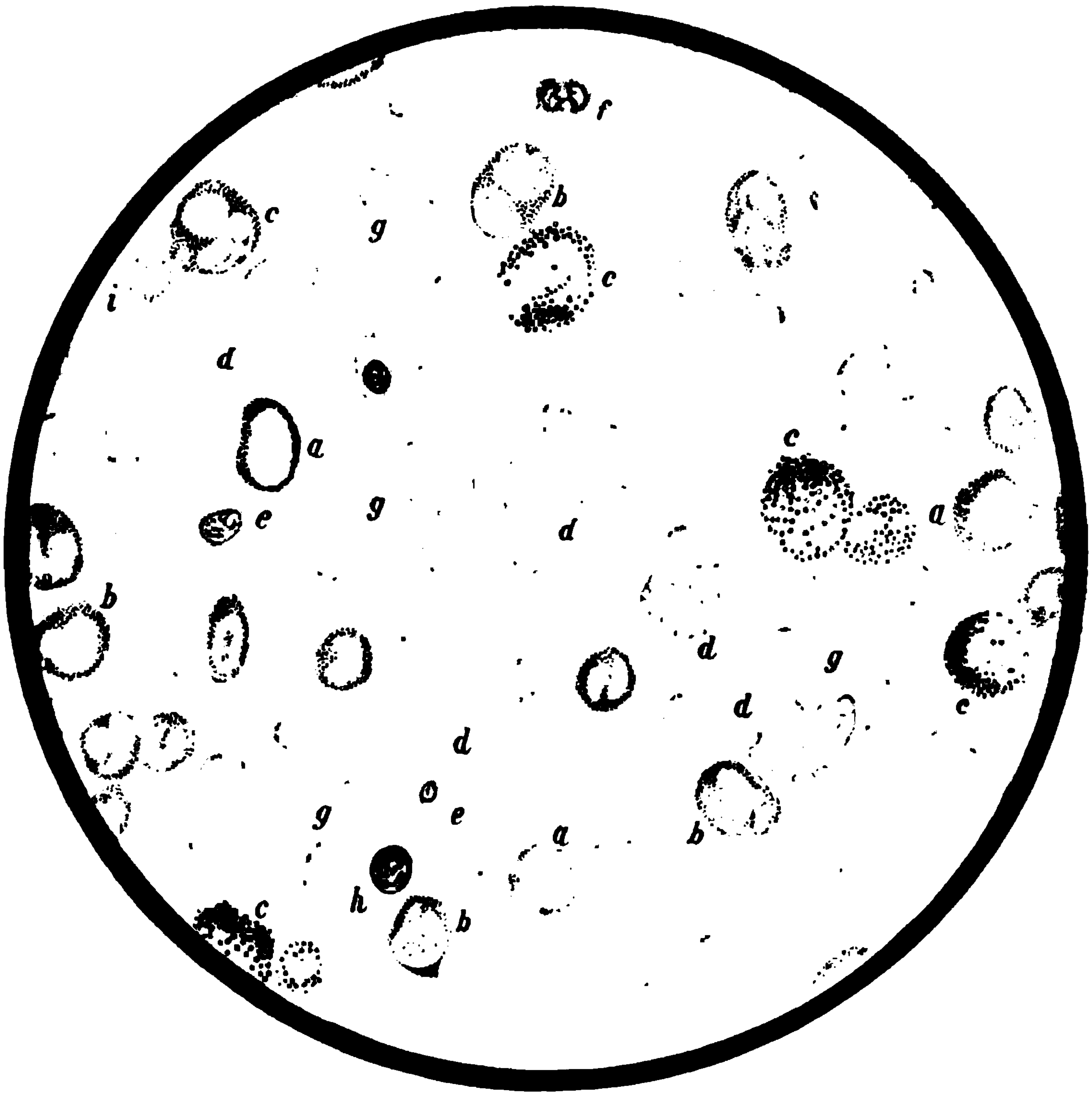
This small table is sufficient to show that not only the individual cases of myeloid leukemia differ from one another, but that the blood-picture of the same case differs considerably at different times.

Case.	Date.	Whites to reds.	Erythroblasts: Erythrocytes.	Percentage of					
				Polynuclear	Myelocytes.	Eosinophiles.	Large mononuclear	Mast cells.	Lymphocytes.
T—e	June 25, 1894	1 : 78	. .	24.3	9.5	4.1	3.0	47.0	12.2
	July 1, 1894	1 : 93	. .	15.2	51.7	4.1	1.7	16.5	10.0
	July 12, 1894	1 : 62	. .	41.5	26.5	8.5	0.5	15.5	7.5
	July 24, 1894	1 : 41	. .	33.3	41.3	2.7	1.0	12.7	8.9
	Aug. 9, 1894	1 : 50	. .	29.8	19.7	8.7	1.0	35.0	5.8
	Aug. 30, 1894	1 : 18	. .	49.4	42.0	2.0	1.9	3.7	1.0
T—h	Nov. 15, 1894	1 : 2.5	. .	7.4	79.4	1.3	0.4	. .	11.4
	Nov. 27, 1894	1 : 2	. .	22.0	70.0	2.8	1.1	0.3	4.8
	Dec. 29, 1894	1 : 3.3	. .	13.6	83.3	1.1	0.2	0.3	2.6
	Jan. 19, 1895	1 : 1.7	. .	20.8	75.0	2.0	0.1	0.2	2.0
P—r	April 16, 1895	1 : 4.2	. .	24.7	65.1	4.5	0.2	0.5	5.0
	April 19, 1895	1 : 5	. .	8.0	80.0	9.0	0.7	1.0	1.3
	May 3, 1895	1 : 3	. .	6.6	82.4	7.1	1.0	. .	3.3
	May 16, 1895	1 : 1.8	. .	10.0	83.4	2.6	0.8	. .	3.1
J—h	Dec. 30, 1899	1 : 4.5	1 : 355	60.3	35.9	1.5	0.5	0.7	2.0
	Dec. 31, 1899	1 : 6	1 : 270	53.0	32.0	5.8	4.5	2.2	3.5
	Jan. 1, 1900	1 : 9	1 : 290	42.6	34.4	8.0	7.5	5.1	2.3
	Jan. 7, 1900	1 : 12.5	1 : 700	47.6	28.0	11.3	8.4	5.0	0.8
	Jan. 14, 1900	1 : 5.5	1 : 620	55.1	25.0	9.1	7.4	1.3	3.0
	Jan. 28, 1900	1 : 8	1 : 600	50.8	27.0	8.2	11.5	2.8	0.5
	June 24, 1900	1 : 7	1 : 180	33.0	50.0	6.6	3.0	1.7	5.6
S—h	July 9, 1900	1 : 9	1 : 125	22.10	58.4	6.37	7.36	1.69	3.79
S—r	July 9, 1900	1 : 3.5	1 : 475	20.0	65.0	5.75	7.5	0.5	1.25

Moreover, special emphasis must be laid on the behavior of the **mast-cells.** In every one of these cases their absolute number is increased, even when their percentage is not higher than the normal average. It is pure accident that the majority of cases here quoted show such a low percentage of mast cells, since usually the relative numbers are much higher. In several cases in which Cabot made accurate counts, he mentions 10 per cent., 8.8 per cent., 3.8 per cent., 2 per cent., 1.5 per cent.; Türk found fluctuations between 6.75 per cent. and 15.53 per cent. in 1 of his cases, between 2.8 per cent. and 11 per cent. in a second, between 4.6 per cent and 5.9 per cent. in a third, and between 7.8 per cent. and 17.67 per cent. in a fourth; Löwit found in these cases 18 per cent., 13 per cent., and 12 per cent. From this, it is evident that the myelemia is characterized by a high absolute and usually high relative mast-cell count.

The fluctuations in these individual cases seem to indicate that the manner in which particular varieties of cells are distributed in a blood-drop, is partly the result of accident, though it can not be doubted that the out-wandering from the bone-marrow is influenced by peculiarities in the disease excitant.

PLATE XIII.



THE BLOOD IN MYELOID LEUKEMIA.

a, Neutrophil myelocytes; *b*, polymorphonuclear neutrophil leukocyte; *c*, eosinophil myelocytes; *d*, mast cells (the vacuoles represent unstained granules); *e*, normoblasts; *f*, normoblast with segmentation-figure; *g*, normal erythrocytes; *h*, megaloblast; *i*, dwarfed polynuclear neutrophil leukocyte. Specimen fixed in formol. Stained with triacid mixture (Leitz, Oil-immer. $\frac{1}{12}$, Oc. I, Tube-length 16).

The *ratio of white to red blood-corpuscles* fluctuates within the widest limits. Still, not so very long since, as is well known, leukemia was differentiated from leukocytosis merely by this ratio, the figures 1–50 or 1–20 being arbitrarily chosen as the boundary dividing the two. To-day we recognize only alterations of the white corpuscles themselves as characteristic for both lymphatic and myeloid leukemia, and even though the ratio W. : R. shows no great deviation, this does not necessarily exclude leukemia. v. Noorden for instance, reports a case of myeloid leukemia in which there was only 1 white to 200 reds. Still, in the majority of cases we find figures which approach very close to 1 : 2 or 1 : 1.

Moreover, in the course of an individual case the ratio W. : R. fluctuates considerably, as is evident from the table just given; in fact, within a few hours surprising alterations have been observed. Thus v. Hayek, for instance, found in his case during the course of one day:

	Temperature.	Reds.	Whites.	
10 A. M.	37.6° C.	2,525,000	122,500	W. : R. = 1 : 20.6
4 P. M.	36.3° C.	2,305,000	235,000	W. : R. = 1 : 9.7

In this case the lowering of the body temperature 1.3° may readily have been of influence, yet independently of anything like this, the blood-picture may change considerably within the shortest interval. From this alone, is evident how little significance is to be attached to the quantitative estimation of the cells.

Even in severe cases of myeloid leukemia the absolute number of red blood-corpuscles is not very markedly decreased. The author saw in complicated cases even sub finem vitæ counts of over 2,000,000, and in Cabot's rich material we find cases of undoubted myeloid leukemia with 5,000,000, 4,877,000, 4,800,000, etc. After long duration of the disease or after intercurrent severe hemorrhages, diarrheas, albuminuria, etc., the number may sink very low, even to one-half million and under.

The proportion of nucleated to non-nucleated red blood-corpuscles is likewise subject to great variations, both in the comparison of different cases and in the course of an individual case at different times, so that in two preparations taken at only short intervals, one may show several examples in every field, the other scarcely any on the whole slide.

In almost all cases we find erythrocytes in a condition of polychromatophilic degeneration—that is, showing granules which stain with methylene blue, as has been described and pictured under "Anemia" (p. 254). Yet, we must expressly insist that we very frequently find

far-advanced cases of myeloid leukemia in which the red blood-corpuscles are absolutely normal in shape, size, and staining properties. Rouleau formation is almost always preserved.

The blood-platelets show no deviations from the normal worth mentioning. The counts which v. Emden made in 2 cases were either normal or varied between one-half and double the normal. Litten asserts that the platelets are always considerably increased in number, and Hayem that they are increased in size.

[The effect of treatment, especially the administration of arsenic, on the blood must always be kept in mind. A. E. Taylor[1] refers to the effects of treatment on the blood in 8 of his series of cases. The influence of arsenic upon the red corpuscles was usually less marked than upon the leukocytes. Three cases showed a complete disappearance of leukocytosis, followed by a relapse and a second disappearance of the excess of white cells. In 2 of the 3 a second relapse, followed by a third disappearance, occurred. The effect of the treatment was quantitative rather than qualitative. The myelocytes were, however, especially reduced in number and proportion. In 1 case there was a return to nearly normal proportions of the different forms of leukocytes; a slight lymphocytosis alone remained.—Ed.]

So much for the peculiarities of the corpuscular elements of the blood.

We have naturally no accurate records in regard to the **quantity of blood.** Estimating by the pulse or the amount issuing from a finger-prick, we have never been able to perceive any striking diminution.

The **color** of the fresh blood-drop is in no way distinguishable from the normal in mild or moderately severe cases; in fact, even when the ratio of whites to reds is 1 : 1, provided the number of reds is not entirely too small, for instance, not less than a million, there is no considerable deviation to the naked eye. In this connection we should add that Virchow's expression "white blood" referred not to the blood during life, but after death. Virchow himself expressly says that in the case in which the "white blood" was found post mortem, an epistaxis shortly before death showed blood of a normal color.

Corresponding to the slight diminution in the number of red corpuscles, we find the **hemoglobin percentage,** according to Fleischl or Gowers, not much below the normal. Not infrequently, in even outspoken cases, we found hemoglobin percentages of 60–70 Gowers.

Still, in the estimation of the hemoglobin by the colorimetric methods,

[1] *Contrib. from the Wm. Pepper Lab. of Clin. Med.,* 1900.

we must remember that the immense number of leukocytes prevents a clear translucent solution of the blood in the water; in fact, they frequently cloud it more or less so that these methods can not be depended upon for absolute accuracy.

The **specific gravity** of the blood is, as a rule, somewhat higher than in other blood diseases with similar hemoglobin percentages, though this is to be expected on account of the comparatively greater richness of the blood in cells. In 1 case in which the hemoglobin was 50 (Gowers) we found the specific gravity to be 1050 (estimated by Hammerschlag's benzol-chloroform method). Dieballa mentions 2 cases of "leukemia myelolienalis" without an accurate description of the blood histology, in which he found the specific gravity 8–14 per thousand higher than the hemoglobin percentage would call for.

More attention has been paid to the **coagulability** of the blood in leukemia than in any other blood disease, and the fact, that the results of the different investigations are very contradictory is due to the non-separation of the different leukemias.

Generally, we find the statement that "leukemic" blood coagulates less readily than normal blood (v. Limbeck, Rywosch and Berggrün, and others), though again others (v. Samson-Himmelstjerna, quoted by Pfeiffer) declare it normal. Unfortunately, we can not decide from the records to which form of leukemia the individual observations refer. We occasionally found it impossible with one patient suffering from myeloid leukemia (Case T) to count the red corpuscles with the Thoma-Zeiss apparatus on account of the extremely rapid coagulation of the blood in the capillary pipet. Yet, in other cases the counting proceeded without difficulty.

It is, *a priori*, very probable that the different varieties of white corpuscles differ considerably from each other in regard to clotting and fibrin formation. Thus from Th. Pfeiffer's work it appears that in cases of myeloid leukemia only a slight increase was noticeable in the fibrin content of the blood plasma (57.9 mm. fibrin = N in 100 cm. plasma in contrast to 39.3 mg. the normal average), while in simple hyperleukocytosis with a considerably smaller total number of whites, almost three times as much was found. According to Lilienfeld, coagulability increases with the richness of the different forms in nuclein, and, according to Minkowski, the lymphocytes are much richer in nucleic acid than the polynuclear cells. The strict separation of the two forms of leukemia and a thorough knowledge of the proportionate participation of the different varieties of leukocytes will possibly aid in explaining the apparently irregular behavior of leukemic blood.

In this regard, Brandenburg's work directed to the chemistry of leukemic blood is very valuable. This shows that the bone-marrow is stained an intense blue by tincture of guaiac, while the lymphatic structures proper, the lymph glands, liver, and thymus fail to give this reaction. From Brandenburg's experiments and his conclusions, it seems highly probable that this difference in reaction is the result of special properties belonging to the nucleoproteids of the bone-marrow cells, which are lacking in those of the lymph cells.

From the statements in the literature in regard to the serum in leukemia, it is impossible to say whether the cases are to be reckoned with myeloid leukemia or not. The figures given in relation to the specific gravity, amount of albumin and dried substance deviate as a rule but little from the normal. Matthes examined the blood post mortem in 1 case of myeloid leukemia, and demonstrated a deuteroalbumose and considerable soluble nucleo-albumin in the serum.

We find in the literature no determinations of the alkalinity of the blood which we can consider as meeting our requirements.

Moreover, the further observations in regard to the chemic peculiarities of leukemic blood are unfortunately but little available for this study, since almost all the cases in question are only designated leukemia and no detailed description of the blood-picture is given. And we have mentioned before that it is exactly in their chemic relations that lymphatic and myeloid leukemia would be expected to show considerable differences. True, very recently attention has been called to this, but it happens that the investigations so far are limited to lymphatic leukemia (see Erben). This investigator is likewise inclined to see a difference in the chemic composition of the blood in the two leukemias, in that he claims the polynuclear cells carry ferments, while the lymphocytes do not. Still, the individual observations on this subject are at present very contradictory and further work toward the eventual solution of the problem would be very desirable.

Among other things we may mention that Magnus-Levy found considerable quantities of uric acid in the blood of 1 case post mortem, and among the other derivatives of nuclein Kossel found xanthin.

An important peculiarity of the blood of myeloid, in contrast to that of lymphatic lenkemia, is the occurrence of Charcot's crystals, observed first by Neumann. These are found normally in the bone-marrow, but in the former disease also in the blood, spleen, and liver in large quantities post mortem (Litten). This finding appears quite reasonable in view of the close relation between the eosinophile cells which are markedly increased in myeloid leukemia and Charcot's

crystals. Since considerable misunderstanding seems to exist, we wish to say that the crystals are never seen in the blood when it is absolutely fresh—that is, just after it has been drawn from the body, but only after it has dried some time under the cover glass. According to Ehrlich, crystallization may occur very rapidly in one case, very slowly in another, though the reasons for this are at present unknown. Westphal took blood by puncture directly from the spleen during life and claims that the crystals were at once visible in it.

THE CLINICAL ALTERATIONS IN THE GENERAL CONDITION AND IN THE INDIVIDUAL ORGANS.

During the long-protracted course of the disease through months or even years, the general condition naturally shows many changes. Yet, not only at the very beginning of the disease, but even after marked development of all the characteristic symptoms, especially the alterations of the blood and the tumor formations, the patient may manifest a surprisingly good **condition of nutrition** and considerable strength, and may complain of almost no subjective symptoms. One of my patients, for instance, a tinner by trade, has for months gone about his work on the house tops, though the symptoms have been fully developed for over a year, and his spleen extends to below the umbilicus. In fact, it is not at all rare for patients to have no idea of the existence of their disease, even when fully developed, till it is casually discovered by a physician consulted for some comparatively insignificant complaint, like epistaxis, pain in the side, or an accident.

When the disease is more rapid in course, or is very far advanced, the patient experiences a feeling of growing weakness. Bodily effort becomes more and more difficult. Among the **subjective complaints** are stitch in the side, shortness of breath, palpitation of the heart, gastric oppression, loss of appetite, and finally pain and tenderness of the different bones, especially the sternum and the long tubular bones.

With protraction of the disease, the **subcutaneous fat** becomes more or less diminished. Toward the end of the disease, after cachexia has developed, a marked emaciation takes place and this is more striking when the abdomen is distended by a very large spleen.

In advanced stages of the disease a more or less marked **anemia** occurs, which is evidenced by the pallor of the skin and mucous membranes, as well as by the blood examination. Still, it would be a mistake to suppose that every case of leukemia must show signs of anemia. Patients are occasionally seen presenting a myeloid leukemia for months

without their appearance or blood showing the slightest symptom of anemia. It has been previously mentioned in the discussion of the morphology of the blood that the red corpuscles are frequently devoid of every anemic change. In the same way cases not rarely occur in which the number is normal or deviates but little from the normal (Cabot, see above p. 651).

In later stages of the disease, especially if protracted diarrhea or frequent hemorrhages occur, we find anemia of the most severe grade. This almost always resembles a simple chronic anemia, though sometimes the presence of megaloblasts and megalocytes changes its character in the direction of progressive pernicious anemia.

Another alteration seen in the general condition is toward the **hemorrhagic diathesis.** In this regard, however, great variations are found in the course of the disease, for instance, periods lasting weeks or months, during which large hemorrhages, particularly epistaxis, may occur daily and again similar periods in which, without special therapy, no hemorrhage occurs.

The hemorrhagic diathesis is characterized by hemorrhages into all the organs, and, though epistaxis is its most frequent expression, hemorrhages from the gums, the digestive tract, into the retina, the skin, the serous membranes, the brain, and the parenchymatous organs, are not rare. These hemorrhages may be the immediate cause of death, either by becoming uncontrollable, as happened in one of Virchow's cases, or by cerebral apoplexy.

The behavior of the **temperature** is entirely unintelligible. A large number of cases have been found apyretic under long-continued clinical observation up to the exitus letalis, others showed fever of varying severity for quite as long periods (see Freudenstein), and finally the same case has shown a normal temperature for months and then a moderately high fever of remittent type (see Temperature Curve, Fig. 8) lasting for weeks. Very high temperature (over 40° C.) which are frequently accompanied by chills, are seen only exceptionally. The second temperature curve here given, is part of one shown by v. Hayek, and from it we learn that the type of fever may be strictly remittent for a long time, like that occurring otherwise only in malaria or septic infection. In regard to this patient we must add that apyretic periods occasionally occurred and that the autopsy showed the case to be uncomplicated. The fever, therefore, seems attributable to the leukemic process *per se*. Naturally, the fever is frequently produced by complications, which are not lacking in leukemia.

The **metabolism** in leukemia has been the subject of numerous

investigations in former and recent times, and though in individual publications it is not always possible to judge the variety of leukemia studied, the general agreement of all the results permits the condition in myeloid leukemia to be judged with sufficient certainty. All the

FIG. 8.—Temperature curve (Case T—e).

investigators, among whom we may mention Pettenkofer and Voit, Kraus and Chvostek, Bohland and Geppert, Magnus-Levy, agree that the *respiratory metabolism* is quite normal.

The investigations thus far (Stricker, Fleischer and Penzoldt,

v. Noorden, v. d. Wey, Magnus-Levy) have shown that there is a considerably increased *proteid metabolism* in chronic myelemia. Still, in the course of the individual case this increased catabolism alternates with a nitrogen equilibrium, in fact, even with the nitrogen retention (v. Noorden). [Taylor[1] found in 1 case a nitrogen balance of intake and output, and normal assimilation and absorption of proteid food. He quotes the authors just mentioned as having found excess of nitrogen elimination, but, on the other hand, 1 case with a negative balance, reported by Mathes, and retention of nitrogen with increase in body weight, reported by Spirig[2] and Moraczewski.[3]—Ed.]

The **urine**, as a rule, shows no striking peculiarities. Different

Fig. 9.—Temperature curve (after v. Hayek).

complications on the part of the kidneys naturally produce their own alterations.

The great interest excited by the enormous amount of uric acid frequently found in the urine in acute lymphatic leukemia has led to investigation of other forms of leukemia, and, as a consequence, more exact estimations have been made in late years.

Magnus-Levy, who reviewed the whole subject a short time ago and added investigations of his own, shows that the relations between the excretion of uric acid and the number of leukocytes in the blood, are very irregular. Great differences are found at different periods in the same case, and at the same stages in different cases; in other words, great and small amounts of uric acid are found with both high and low leukocytic counts. Yet, in this question particularly careful attention has not been bestowed on the morphologic separation of the different

[1] *Contrib. from the Wm. Pepper Lab. of Clin. Med.*, 1900.
[2] *Zeit. f. klin. Med.*, 1894. [3] *Virch. Arch.*, 1898.

leukemias. Further, the difference in the amount of nuclein in the different varieties of white blood-corpuscles recognized by all observers forcibly suggests the reason for these variations.

For the same reason the scanty data on the excretion of nitrogen as urea, as xanthin bodies, etc., are not available. We may mention that albumosuria has been found by Köttnitz and v. Noorden, by each in 1 case. Further, v. Noorden found large amounts of nucleo-albumin in 2 cases of myeloid leukemia.

Among the abnormal non-nitrogenous substances, v. Noorden observed in 1 case a transitory excretion of acetic acid.

Among the inorganic substances phosphorus is particularly noteworthy. Yet though phosphoric acid has been found in large amounts in the urine in acute lymphatic leukemia, the literature fails to show whether this is true also of myeloid leukemia.

[Taylor[1] found in 3 cases marked increase of neutral sulphur in the urine. The interpretation of this condition is uncertain.—ED.]

Among the organic alterations attracting the attention of the investigator, the **enlargement of the spleen** stands out most conspicuously. Very often this is the direct or indirect cause of the patient consulting the physician, and even on the first examination an enormous enlargement is frequently found. Cases are not at all rare in which the spleen extends to the right a half-hand's breadth beyond the middle line and downward almost to the symphysis, apparently resting on the left brim of the pelvis. The abdomen is distended and is entirely out of shape, the left side being very hard, prominent, and the right compressible and less prominent. The abdominal wall, almost devoid of fat, frequently allows the superficial surface and notched border of the spleen to be palpated. As a rule, the spleen is extremely hard, but rarely it is soft. In 1 case of Ehrlich's it was, in places, diffluent. Dry friction râles, corresponding to the respiration, are frequently heard on auscultation over different areas or even over its whole extent.

Though in the majority of cases of myeloid leukemia the splenic tumor is the most striking clinical symptom, it is by no means always present. For instance, Litten mentions a case in which the spleen was only very slightly ("ganz minimal") enlarged.

Though transitory reductions of 1–2 cm. in breadth and length are observed after the organ has reached a considerable size, complete retrogression of the enlargement occurs only exceptionally. Such a case was recently described by Kraus in which all the symptoms together with the splenic tumor, disappeared under the influence of an infectious disease.

[1] *Contrib. from the Wm. Pepper Lab. of Clin. Med.*, 1900.

Swelling of the lymph glands is observed much less frequently than the splenic tumor. The distribution of the affected glands holds no relation to that seen in lymphatic leukemia, in fact, from the reports accessible, they seem more common in the inguinal and axillary regions than in the neck, the site of predilection in the latter. We sometimes, too, find enlargement of the lingual follicles, the tonsils and the salivary glands. The skin over the swollen glands is neither hyperemic nor adherent, palpation is not painful.

We must mention also several symptoms produced by the impalpable internal granular tumors. On account of the unlimited diversity in localization, it would naturally be impossible to enumerate all the resulting conditions, consequently we are constrained to recall only the more frequent. Pressure on the large vascular trunks may lead to stasis in almost any organ, and general stasis may be produced by pressure on the largest vessels due to swelling of the mediastinal glands. Compression of a bronchus may produce marked disturbances of respiration, as well as anomalies evident to percussion and auscultation. According to F. A. Hoffmann, paralysis of the recurrent nerve, due to pressure, has been observed. Leukemic infiltration of the larynx has produced stenosis (Laache), and also, through compression of the esophagus, dysphagia. The development of lymphomata has been the cause of disturbances of nerves, and their development in the orbit, the cause of exophthalmos (Laache).

Isolated cases of myeloid leukemia run their course without enlargement of either external or internal lymph glands.

The **liver** is frequently enlarged to palpation. Its surface is smooth, its consistence firm.

Circulatory symptoms peculiar to this disease have not been observed. Symptoms described under the different forms of anemia—irritability of the heart, hemic murmurs, hydropericardium, are naturally found in cases accompanied by severe grades of anemia.

Marked hyperemia of the large and small abdominal veins is seen as a result of the enormous distention of the abdomen. In late stages we find a more or less marked edema of the lower extremities.

Respiratory symptoms are manifest in the majority of cases. Dyspnea is usual and may be produced by compression of the lungs and bronchi, through enlargement of the spleen and glands. The disturbances of the circulation also lead to disturbances of bronchial secretion and thereby to obstinate bronchitis. According to F. A. Hoffmann, the sputum shows in all cases enormous numbers of eosinophile cells. Serous or hemorrhagic exudations may be found in the pleural

cavity as the result of severe stasis, or the latter as the result of a general hemorrhagic diathesis. Examination of the exudate in 1 case by Ehrlich showed all the morphologic elements of the blood to be present.

The **digestive organs** are variously affected. The appetite is frequently influenced, through the feeling of fulness produced by the enlargement of the spleen and liver. With this anorexia, nausea, eructation, and sometimes persistent vomiting are associated. Laache reports intense thirst in several cases. When the ingestion of nourishment remains unimpaired, the normal weight is preserved for months, which would indicate that the functions of the stomach and intestine, as well as assimilation, are not disturbed.

Sometimes a transitory hindrance to the taking of nourishment is produced by a severe stomatitis, associated with hemorrhages and ulceration of the gums.

Diarrhea is very frequent. It is sometimes mild and transitory, but again extremely severe and obstinate, and leads to rapid loss of strength. The stools are sometimes simply diarrhetic in character, though again contain blood. In the latter cases, the most careful dietetic and remedial regulations are often insufficient to control the intestinal hemorrhage.

[As bearing upon the gastro-intestinal symptoms it may be recalled that ulceration in the gastro-intestinal tract has been noted by many writers. Saundby[1] reports 2 instances, 1 of them being fatal and showing at autopsy healed ulcers in the intestines, and 1 irregular superficial ulcer that had not healed.—ED.]

In conclusion we must mention the ascites which frequently occurs, especially toward the termination of the disease. Milchner examined the cellular constituents of the fluid and found that, as in Ehrlich's pleural exudate, all varieties of white blood-corpuscles were present, though mast cells predominated to the extent of almost 50 per cent.

Skin.—The skin of a well-developed case is usually dry, lusterless, pale and shows an inclination to all forms of exanthemata, erythema, acne, furunculosis, and urticaria. In lymphatic leukemia the skin is very frequently the seat of lymphomatous tumors, in myeloid leukemia this is by no means so frequent, yet several times it has been observed. For instance, Hindenburg found in one of his cases a tumor the size of an apple in the skin of the thigh.

As in cachectics generally, severe sweating is common in the late stages of myeloid leukemia. This increases still more the suscepti-

[1] *Brit. Med. Jour.*, Jan. 5, 1900.

bility of the skin to various diseases, and aids in the production of general prostration.

The **central nervous system** has been found variously affected in leukemia, and we have very thorough descriptions (even though few in number) of the symptoms. In the literature that we have seen, all the descriptions referred to lymphatic leukemia; a detailed study of the symptoms, therefore, in myeloid leukemia is lacking. Still, we can assume that the symptoms, produced by hemorrhage into or degeneration of the nerves, are quite as frequent and as severe as in lymphatic leukemia. Though the alterations dependent on infiltration and tumor formation are much more rare in myeloid leukemia since, as has been previously explained, there is much less tendency to "metastasis."

The same is true of the clinical symptoms referable to the **organs of special sense.** Some of the functional *alterations in the eye*, as well as those seen with the ophthalmoscope, correspond to those found in severe anemias (see this volume, p. 474). They are the result of the hemorrhagic diathesis and are found especially in those cases manifesting a severe hemorrhagic character. Since anemia is by no means the rule in myeloid leukemia, and frequently reaches, at most, a slight grade, many cases show no ocular disturbances. The white and whitish-yellow, sometimes elevated spots on the retina, described by ophthalmologists in leukemia, belong as far as we can see to lymphatic leukemia, and are, from an anatomic standpoint, to be regarded as round-cell infiltrations or mere extravasations (Schmidt-Rimpler). Sticker observed in 1 case of myeloid leukemia clouding of the vitreous, large extravasations of blood, swelling, and clouding of the papilla, and an extensive detachment of the retina of one eye.

Communications in regard to disease of the *ear* are less frequent. [Steinbrügge and Pepper long ago referred to deafness as among the occasional symptoms of leukemia.—ED.] We owe to Schwabach a complete presentation of this subject. Subjective noises, symptoms of vertigo, disturbances of hearing to complete deafness in both ears, are noted not very rarely, even though in the very great majority of cases no aural complications were observed. During life hyperemia of and hemorrhage into the tympanum and into the external meatus have been seen in several cases.

As to the **sexual organs,** priapism is especially frequent (see Sticker's case). With increasing cachexia the loss of potentia virilis naturally occurs. In advanced stages there is complete cessation of the menses. Yet, in the recent literature, several cases have been described in which women with well-developed leukemia conceived and went through a normal labor.

PATHOLOGIC ANATOMY.

THE autopsy findings in myeloid leukemia differ scarcely at all to the naked eye from those in lymphatic leukemia, excepting in the bone-marrow. We shall content ourselves, therefore, with a brief description, referring for fuller details to that in the previous section.

We find, as a rule, a severe general **anemia,** and in many organs more or less extensive hemorrhages. According to the autopsy reports, the brain and spinal cord seem to be the particular sites for hemorrhages, even in those cases in which intra vitam not the slightest clinical symptom was evident. Next in order we find the retina the most frequent seat of hemorrhages, and following this the serous membranes and the skin.

The **blood,** post mortem, shows such a peculiar appearance, even macroscopically, that Virchow was led to the diagnosis of a particular disease and derived the name from it. The classical description given by Virchow in this first case may, therefore, be given: "The heart was filled to distention with large greenish-yellow clots loosely attached to each other which broke up under the touch, were not adherent to the walls, and appeared like hardened pus. Similar coagula were found in the aorta, the large arteries and veins, and the veins of the lower extremities. Thin-walled veins looked exactly like canals filled with pus. The surface of the heart and cerebral membranes, the veins of which were markedly distended by their pus-like contents, seemed to be covered with solid yellowish-white cords. The contents were free in the vessels and the walls were in no way altered." The changes in the blood are not so marked in all cases, in fact some come to section showing the blood brownish red or brown, with the pus-like clots occurring only in specks.

Another blood finding in myeloid leukemia is Charcot-Leyden crystals. According to Neumann they occur regularly and exclusively in this form of leukemia.

(For the appearance of the blood-cells, see the clinical section.)

According to Neumann's thorough investigations, the organ which even to the naked eye differentiates myeloid from lymphatic leukemia,

is the **bone-marrow.** As far back as 1869, Neumann taught that in the cases of leukemia in which the mononuclear and polynuclear leukocytes of the blood are characterized by their size and their peculiar protoplasm, the bone-marrow shows pyoid characteristics. It is pus yellow in color, becomes red after exposure to the air, and is soft though tenacious.

This alteration of the bone-marrow is not found in every case in all bones, but principally in the sternum and long tubular bones. Mosler described a case in which the whole skeleton showed such a condition "exactly like that seen in suppurative osteomyelitis."

The microscopic examination of the bone-marrow shows a picture very similar to that seen intra vitam in the blood.

Charcot-Leyden crystals are also very numerous in the bone-marrow, though here they represent a normal finding.

From what has been said, therefore, it is evident that the bone-marrow shows the same differentiation of the two leukemias post mortem as the blood intra vitam.

The **spleen** shows, macroscopically, very different conditions in the different forms of leukemia. In the very great majority of cases of myeloid leukemia it develops to immense size, so that its weight may reach 8 or even 10 kg. In both myeloid and lymphatic leukemia this enlargement usually represents a simple hyperplasia of the organ. The capsule is thickened and in many places adherent to the neighboring organs. The larger the tumor and the longer the disease has existed, the harder the organ. If the duration of the disease was comparatively short, the spleen may contain considerable blood, but after a very chronic course it is apt to be dry. On section the follicles are not conspicuous. The connective tissue is considerably increased.

If cover-glass preparations are made from the teased spleen, we find numerous elements belonging to bone-marrow tissue which are never seen either normally or in lymphatic leukemia.

This **myeloid metamorphosis** of the spleen was first remarked by Ehrlich, and since then it has been frequently described as a characteristic finding in myeloid leukemia. Whether it is diffuse or circumscribed has yet to be shown by further investigations, though we expect this to be decided shortly on account of the method described by Benda, of staining the neutrophile granules in sections.

It may be mentioned here that very recently a myeloid transformation of the spleen and lymph glands has been observed in other conditions than myelemia. Frese, for example, described a case of carcinoma of the bone-marrow in which a myeloid metamorphosis of the spleen

was evident, and he is inclined to see in this a vicarious action of the spleen in order to make up for the disturbed function of the bone-marrow. Dominici investigated this subject experimentally, and succeeded in producing or finding a myeloid metamorphosis of the spleen in guinea-pigs in different conditions—namely, during pregnancy, post-hemorrhagic anemia, after infection with bacillus typhosus, and experimental tuberculosis.

We are not yet in a position to explain fully the significance and manner of origin of this myeloid change, yet it is practically beyond doubt that the enormous increase of bone-marrow cells in the blood is to be referred in part to a proliferation in this newly developed myeloid tissue.

Apart from the occurrence of this myeloid tissue in the spleen, we are completely in the dark about the nature and significance of the splenic tumor in myeloid leukemia.

What has been said in regard to the spleen is applicable to both the peripheral and visceral **lymph glands.** According to Virchow, their enlargement, which may vary in extent and distribution in different cases, represents pure hyperplasias associated with connective-tissue overgrowth. A myeloid metamorphosis is also frequently found which indicates the participation of the glands in the overproduction of bone-marrow cells.

Corresponding to the description of the clinical symptoms, the **liver** is found considerably enlarged in a great number of cases. This is usually the result of a pure hyperplasia of the liver tissue. Yet how far a lymphomatous development, such as is seen in lymphatic leukemia, may be responsible can not be said on account of the lack of properly investigated material. Virchow expressly insists that his cases were lymphatic leukemia.

It is, moreover, extremely difficult from the autopsy reports at hand to decide how far the general tendency to **lymphomatosis,** characteristic of lymphatic leukemia, is present in myeloid leukemia. Yet it seems to me certain that the tendency exists in a much less degree in this disease, even though it has been described in several well-authenticated cases.

Apart from the alterations produced in other organs by the anemia, hemorrhages, etc., we find but few deviations from the normal which can be brought into relation with the leukemia. We may mention, for instance, the absolutely negative finding in the respiratory organs, even in cases in which the patient has been tormented for months by severe dyspnea and violent, almost uncontrollable coughing spells. On the

part of the heart, Ehrlich mentions the discovery of an ulcerative endocarditis, though its dependence on the leukemia is not evident. Corresponding to the severe diarrheas frequently observed during life, diphtheritic ulcers of the intestine, especially the large intestine, are sometimes found.

Excited by the observations in progressive pernicious anemia, investigations of the **central nervous system** have been made in leukemia, several of which (Nonne) pertain to myeloid leukemia. In 1 case a more or less advanced acute myelitis was found irregularly distributed over circumscribed areas, together with sclerosis of isolated foci in the posterior columns.

On the part of the **kidneys** we may mention the uric-acid deposits, which undoubtedly stand in very close relation to the disease.

The findings in the **eye** correspond to those seen with the ophthalmoscope and described in the symptomatology.

From Schwabach's previously quoted investigations it appears that the **ear** is frequently affected in leukemia. The great majority of cases studied by him, which, however, were principally lymphatic leukemia, showed hemorrhages or their results, or lymphocytic accumulations. The lesions are found in the external and middle ear, though even more commonly in the nervous apparatus of the organ.

COURSE AND DURATION. PROGNOSIS.

THE disease begins insidiously, and all the cases reported so far came into the hands of the physician only after all the symptoms were well developed. Even at this time, as previously stated, the general condition of the patient may be very good. Moreover, without any improvement in the leukemic symptoms, in fact even when they continue to increase in intensity, the patient's strength may be preserved for months or years. True, sometimes even in the early stages, severe accidents happen unexpectedly or death itself may occur as the result of a severe hemorrhage or cerebral apoplexy. The fatal termination occurs, as a rule, early, when severe anemia and a rapid diminution of strength is produced by persistent hemorrhage, fever, or diarrhea. The exitus lethalis then occurs under symptoms of general marasmus, severe subjective disturbances of every kind, and various complications, like pleurisy, peritonitis, and general anasarca. In some cases severe cerebral symptoms, like delirium, maniacal paroxysms or coma, act as the forerunners of approaching death.

Yet, even when apparently far advanced, we sometimes observe a retrogression of the severe symptoms and a renewal of the strength, for instance, the proportion of whites to reds becomes more favorable, the enlargement of the different organs, especially the spleen, retrogresses, the fever ceases, nourishment improves, strength returns, and some patients are even able to take up again a strenuous occupation. These variations in the severity of the symptoms occur repeatedly in individual cases, just as they are apt to do in every disease running a chronic course. Yet they are not to be compared with the complete disappearance of the symptoms which we occasionally see in progressive pernicious anemia, for the myeloid leukemia always continues to be evident in the blood, even when the subjective and the objective symptoms become decidedly less marked.

The literature so far shows no case of myeloid leukemia accurately observed which ran an acute course. Almost all the cases of acute leukemia were lymphemias, and the majority described as myeloid leukemia are to be explained by the confusion of the large lymphocytes

with the large mononuclear leukocytes. Cabot's 2 cases alone, which have been previously mentioned on account of their relation to each other (see p. 648), seem to be true myelemia. [Billings and Capps[1] contribute a valuable article on acute myelogenous leukemia, reporting 1 case under their own observation. They review the literature very thoroughly, referring first of all to the cases of acute leukemia collected by Fränkel up to 1895, and to the conclusion of this author that all cases of acute leukemia are lymphatic. A number of authors have recently objected to this view. Billings and Capps have collected 7 instances of acute myelogenous leukemia besides their own and 2 others which are rather doubtful. Among the conclusions drawn from the analyses of these 8 cases are the following: The disease begins abruptly like an infection. In 4 there was an inflammation of the throat and in 3 a necrosis of the jaw or palate. In 6 the glands were moderately enlarged, the cervical group usually being affected. The spleen was felt in every case, but in only 2 did it extend more than a finger's breadth below the ribs. Hemorrhages were present in every case in which the history was obtained and irregular fever was usually present. Severe and rapidly developed anemia is the rule, but irregularity of the red cells is less conspicuous than in pernicious anemia. The white cells number from 16,000 to 540,000; the average being much below that of chronic myelogenous leukemia. The diagnosis must be made from the following conditions:

1. Chronic myelogenous leukemia with an acute exacerbation (Reimann). The history and the great enlargement of the spleen are the principal distinguishing points. 2. Lymphatic leukemia, complicated by an intercurrent infection (Hirschlaff). The presence of polynuclear cells in abundance and the small number of myelocytes furnishes the distinction. 3. Acute lymphatic leukemia with predominance of large mononuclear cells. The absence of myelocytes is the principal distinguishing feature. 4. Acute infections with grave and rapid anemia, and with the presence of nucleated red cells and myelocytes. Leube reports such a case and thought it due to irritation of the bone-marrow. The white-blood count is generally lower than in leukemia. 5. Exacerbations of pernicious anemia. Prior examination of the blood would furnish the distinction. Billings reported a case in which the leukocytes numbered 34,000 two days before death, and there were 29.4 per cent. of myelocytes. 6. Tumors of the bone-marrow and the enormous number of nucleated red cells. The chronic course, gradual anemia, and small number of myelocytes characterize such cases.

[1] *Amer. Jour. of the Med. Sciences*, Sept., 1903.

In studying these cases there is always difficulty in separating large mononuclear cells from the myelocytes. A rule which the author has adopted was to consider as myeloid cells any large mononuclear cells seen in association with large numbers of myelocytes of the same size, when many of the mononuclears showed indistinct granulations.

Turck[1] reports a case of acute myeloid leukemia with green color of the bone-marrow. The patient was a man who had previously been healthy, but during six months had grown pallid and had suffered from hemorrhages from the gums. Following this there was a rapid increase in the severity of his general condition. There were ecchymoses under the skin and conjunctiva, and a hemorrhagic neuroretinitis. The spleen was moderately enlarged. The blood examination showed 1,000,000 red cells without morphologic change, and 19 per cent. of hemoglobin. The leukocytes numbered 40,000, of which 40 per cent. were myelocytes, 32 per cent. polynuclears, and 15 per cent. lymphocytes. The anemia increased and death ensued without the development of fever. The essential lesion found at the autopsy was a diffuse grass-green coloration of the marrow in the vertebral ribs, sternum, the proximal portion of both femurs, and a preparation from the marrow showed it composed almost entirely of neutrophile myelocytes.—Ed.]

In spite of the indefiniteness of its beginning, we can say that the entire duration of the disease is at least six months. As a rule it lasts longer than a year. In one case described by Virchow and in another by Hindenburg it lasted four years.

The **prognosis** is absolutely unfavorable. Not one of the cases mentioned in the earlier literature as cured will stand the tests necessary to the diagnosis of myeloid leukemia. We must, therefore, say that myeloid leukemia is incurable. It leads to death in a comparatively short time despite all therapeutic measures.

[1] *Deutsch. med. Woch.*, No. 22, 1903.

COMPLICATIONS.

We have seen that myeloid leukemia readily draws into participation, principally by hemorrhage and enlargement, other structures besides the blood and blood-making organs. Moreover, what is not surprising in such a chronic affection, other diseases may be added which have no relation to the leukemic process *per se*, but arise only on account of the favorable soil created by it. We may mention especially phthisis pulmonum, endocarditis, nephritis, amyloid disease of the liver and kidneys, and diabetes.

[Elsner and Groat[1] report a case of leukemia complicated by the development of tuberculosis. With the appearance of the tubercular manifestations, the number of leukocytes diminished and the neutrophile cells, and lymphocytes increased proportionately while the myelocytes showed a corresponding decrease. A case similar to this was reported by Sturmdorf,[2] who called especial attention to the fact that there was a change in the proportion of myelocytes and neutrophile cells during the febrile attacks to which the patient was liable. In these cases the tubercular process involved the larynx as well as the lungs. Hirschfeld and Tobias report a third case, and have collected 10 cases, not including that of Sturmdorf, making a total of 12 cases so far reported. In their own case the number of leukocytes diminished, though not so markedly as in others, at the onset of the tubercular trouble. Neither was there the striking change in the leukocytic count.—Ed.]

These complications excite but little interest. Still, we are attracted by the peculiar influences exerted by acute infectious diseases on the leukemic process. Several cases of myeloid leukemia have been described in which all the symptoms of the disease markedly improved under the influence of an acute infectious disease. These cases were seen in complication with phthisis pulmonum, influenza, sepsis, and erysipelas. *Erysipelas* especially has shown a very peculiar modifying influence on the whole disease. For instance, among others, Richter described a case in which a decrease in the number of white blood-

[1] *Amer. Jour. of the Med. Sciences*, March, 1901. [2] *Ibid.*, August, 1901.

corpuscles from 380,000 to 29,100 took place immediately after an outbreak of erysipelas. The general condition also improved considerably, the fever ceased, and nutrition became better.

The most pronounced case of this kind was recently described by E. Kraus. In this case a complete retrogression of all the leukemic symptoms, even those of the blood, followed the appearance of a circumscribed erysipelas. The erysipelas led to a subacute diplococcus and streptococcus infection, an old tuberculosis became generalized, and the patient died about a month after "cure" of the leukemia. At autopsy, apart from a moderate-sized tumor of the spleen, there was no anatomic sign of the leukemia; even the portion of the bone-marrow examined was found normal.

Acute infectious diseases may likewise change the picture—especially the blood finding—in an opposite way, namely, by the production of a marked leukocytosis, which completely transforms for a time the previously pure leukemic picture.

Nothing decisive can at present be stated in regard to the relation of myeloid to lymphatic leukemia, particularly as to the possibility of transition of one into the other. Such a transition has been several times asserted, yet so far we have no positive evidence from an accurate morphologic analysis of the blood in the different stages.

Thus, for instance, a frequently quoted assertion of v. d. Weys says that he found in one case of positive myeloid leukemia at the beginning of July, 65.5 per cent. myelocytes, and in August and September 96.3 per cent. mononuclear non-granular white blood-corpuscles, which he believed to be lymphocytes. From the observer's description, however, there is no evidence contrary to the assumption that this 96.3 per cent. of mononuclear non-granular cells represents entirely or partially the ordinary large mononuclear leukocytes (Naegeli's "myeloblasts"). In fact, this picture may have represented a process observed in severe anemias, namely, complete disappearance of the neutrophile granules under the influence of general marasmus.

For the relations of progressive pernicious anemia to leukemia suggested by Litten, see p. 304.

DIAGNOSIS.

For the diagnosis of a disease which is differentiated from others only by the appearance of the blood, the microscope is an absolute essential. A further essential is the dried stained preparation in order to differentiate the various granulated and non-granulated cells, especially the large mononuclear leukocytes and lymphocytes.

Yet, it can not be denied that in advanced cases the examination of the fresh unstained blood may be sufficient to make a diagnosis, not only of leukemia, but even the kind of leukemia. With experience we can learn to differentiate the various granulations even in unstained blood, after we have been taught their appearance in stained specimens. Yet, in obscure cases requiring a more careful study of the individual white blood-corpuscles, the dried preparation and a triacid stain or an equivalent are essential.

The statement of all the points in the diagnosis would require a repetition of what has been thoroughly discussed in the general part (p. 125), and in the Special Symptomatology (p. 649). We will, therefore, content ourselves with a brief review of the most important things necessary for a practical diagnosis, and refer for further study to the two chapters named.

Independently of other clinical symptoms, the following are necessary for a diagnosis of myeloid leukemia:

1. The granular mononuclear leukocytes (Ehrlich's myelocytes) must constitute a considerable number of all the white blood-cells. Their appearance in the blood is always somewhat abnormal, yet in non-leukemic cases, even when their percentage is moderately high, their absolute number is small, in fact far below the smallest numbers ever observed in myeloid leukemia. The diagnostic significance of these cells, therefore, is greater, the greater the deviation of W. : R. from the normal.

2. The eosinophile mono- and polynuclear cells must be considerably increased. Their percentage may not be greater than a high normal (3–4 per cent.), yet their actual number per cubic millimeter is

incomparably greater than in the most marked cases of pure eosinophilia yet observed.

3. The mast cells must show a great absolute increase.

4. Nucleated red blood-corpuscles of especially normoblastic type must be readily found.

With these qualitative alterations of the morphologic elements of the blood, the diagnosis of leukemia is assured. Yet, Ehrlich's requirement must not be forgotten, namely, that all of these characteristics must be present simultaneously.

[Referring to the difficulty in diagnosis of leukemia from the morphology, Lipowski[1] refers to a case of carcinoma of the bowel with marked leukocytosis and pronounced anemia. The white cells were present in a proportion of 1 : 18 of the red. Nucleated red corpuscles and myeloblasts were found, and, in the absence of a tumor or glandular swelling, a diagnosis of leukemia was made. The condition of the blood he attributes to secondary metastasis in the bone-marrow and recalls the case of Nothnagel, in which the picture of lymphatic leukemia resulted from lymphosarcoma metastases in the bone-marrow. In his own case the white cells were neutrophilic, not a single nongranular cell or eosinophile being found. It is evident that Ehrlich's strict requirements were not fulfilled in this case.—ED.]

As is evident from the data given under the symptomatology, the simple quantitative estimation of the proportion of whites to reds which was previously considered as the only essential, is not sufficient. For, in the first place, there are cases of genuine myeloid leukemia in which the proportion of W. : R. was very high; for instance, 1 : 200 (v. Noorden) and in the second, there are cases of simple neutrophile leukocytosis in which W. : R. showed a decided decrease 1 : 50, 1 : 30, 1 : 25, 1 : 15.

In the same way the purely clinical symptoms have been proven insufficient for a diagnosis. The enlargement of the spleen and lymph glands, the tenderness of the bones, the hemorrhages are, it is true, adapted to aid in the proper diagnosis, yet nothing can be proven by them. In this connection it is worth while recalling the case mentioned several times previously, which presented the characteristic blood-picture without one of these gross clinical symptoms.

Finally, therefore, the examination of the blood is the only criterion in the differentiation of all the conditions which show a similarity in their general clinical symptoms with leukemia, as severe anemia, septic processes, intermittent fever, etc.

[1] *Deutsch. med. Woch.*, May 24, 1900.

A negative blood-finding, however, is to be viewed with caution when there is the slightest suspicion that an intercurrent disease; as, for example, sepsis may be masking the leukemia. For, as the case described on p. 671 shows, the picture of myeloid leukemia may thus be completely obliterated. Still, in most cases one or more of the cardinal symptoms always remain recognizable to strengthen or awaken the suspicion of myelemia, though even then a positive diagnosis may only be made after the transit of the complication.

TREATMENT.

THE discussion of the therapy unfortunately consists only in the enumeration of the futile attempts to do something. In this regard there is not the slightest difference between lymphatic and myeloid leukemia, and we may refer, therefore, to the chapter on the former (see p. 613).

Still, on account of the much greater frequency of the splenic tumor in myeloid leukemia, we wish to expressly state that splenectomy as a therapeutic measure is not to be considered. In fact, the operation itself has resulted in death in the majority of cases due either to the immense size of the tumor or fatal hemorrhage. Yet, even when the operation was without fatality, not the slightest influence was produced on the course of the disease. Further, all the theoretical considerations in regard to the significance of the splenic tumor are absolutely against splenectomy; consequently recent writers (F. Kraus, Braun, *et al.*) are justified in placing leukemia among the contra-indications to splenectomy.

Expectations that remedial measures will be found for leukemic conditions are based on the favorable influence of intercurrent diseases (see p. 670). Experiments in this connection must be directed to the finding of weak infections or intoxications capable of checking the leukemic process without endangering the life of the patient. The experiments made so far, however, have unfortunately proved futile.

[The editor's experiments with vaccination have proved the futility of this procedure.—ED.]

X-ray Treatment.—Some remarkable results have been achieved by the *x*-ray treatment of pseudoleukemia and leukemia.

Pusey[1] reported a case of pseudoleukemia symptomatically cured, and a little later Williams[2] reported 3 cases 1 of which showed remarkable improvement.

The same year, Senn[3] reported 2 cases symptomatically cured. Dunn[4] reported a similar case in which, after a year's interval, no

[1] *Jour. Amer. Med. Assoc.*, 1902, p. 911.

[2] *The Röntgen Rays in Med. and Surg.*, 1st edition.

[3] *New York Med. Jour.*, 1903, p. 665. [4] *Internat. Jour. of Surg.*, 1903, p. 315.

recurrence was observed. Rodman and Pfahler[1] reported 4 cases under treatment, all of them improving. Butler[2] reported 2 cases with marked improvement. Childs[3] recorded 1 case improved.

The literature of the treatment of leukemia is less extensive. Senn[4] reported the apparent cure of a case of myelogenous leukemia. The blood examinations were not made with sufficient detail, but there was an evident diminution in myelocytes and in the volume of the spleen. One of the cases reported by the same author[5] as pseudoleukemia seems to have been leukemia. The number of leukocytes in this case was 230,000 per c.mm., of which 78.75 per cent. were small lymphocytes and 14.25 per cent. large mononuclear lymphocytes. Both this case and the other of pseudoleukemia reported by Senn were in good health on March 20, 1904, according to a letter from Senn to Grosh and Stone. The case of myelogenous leukemia reported by Senn was on the same date again under treatment, having suffered a moderate relapse.

Grad[6] reported a case with improvement. The details, however, are imperfectly recorded. E. J. Brown[7] reported an instance of myelogenous leukemia symptomatically cured. The blood examination at the beginning of treatment showed 2,600,000 red corpuscles, 800,000 white corpuscles. The differential count of the latter being polymorphonuclear 40 per cent., myelocytes 40 per cent., eosinophiles 8 per cent. The hemoglobin was 65 per cent. The spleen extended from the seventh rib to two-fingers breadth below the umbilical line. Arsenic and iron were administered, and x-ray treatment applied to the splenic region twice weekly. After two months, the leukocytes fell to 58,000; later they increased to 129,000, and again decreased to 44,360. Two months later, they numbered 7,894; the red corpuscles 4,690,000, the hemoglobin was 95 per cent. The patient's weight increased to normal. The albuminuria which was present during the treatment disappeared. Dermatitis had been present once or twice over the splenic region during the treatment. There were, however, no toxemic symptoms nor any rise of temperature such as occurred in Senn's case. Dock[8] suggested that an accidental infection might have something to do with the result of the treatment. Grosh and Stone[9] reported a case in which

[1] *Phila. Med. Jour.*, 1903, p. 971.
[2] *Louisville Monthly Jour. of Med. and Surg.*, 1903, p. 463.
[3] *Med. News*, 1904, p. 145.
[4] *Med. Record*, Aug. 22, 1903.
[5] *New York Med. Jour.*, April 25, 1903.
[6] *Jour. Adv. Therap.*, Jan. 1904, p. 30.
[7] *Jour. of Amer. Med. Assoc.*, March 26, 1904.
[8] *Ibid.*, April, 1904. [9] *Ibid.*, July 2, 1904.

during June the average blood-count was 2,600,000 red corpuscles, 940,000 leukocytes, and 45 per cent. hemoglobin. In July the average was 3,600,000 red corpuscles, 620,000 leukocytes, and 64 per cent. hemoglobin. The following November the leukocytes were 175,000, the hemoglobin 70 per cent. In December, 135,000 leukocytes, 65 per cent. hemoglobin. In January, 2,600,000 red corpuscles, 211,000 leukocytes, 60 per cent. hemoglobin. In February, the count was practically the same. During all of this time there was a high percentage of myelocytes, the range being from 27.9 to 52 per cent. The eosinophiles ranged from 2.5 to 8.5 per cent. Arsenic treatment was instituted in June, 1903, the exact quantities, however, not being stated. *X*-ray treatment was begun February 21st, and during the treatment small doses of arsenious acid were taken internally. The subsequent blood-counts were as follows: March 10th, 2,507,000 red, 52,600 white, 55 per cent. hemoglobin. March 18th, 14,918 leukocytes. March 22nd, after 20 treatments, 3,578,780 red corpuscles, 11,480 leukocytes, 70 per cent. hemoglobin. At this time the treatment was stopped on account of a general erythematous eruption. The spleen was somewhat smaller. March 26th, the leukocytes numbered 11,360. April 10th, 10,600. During this same period the myelocytes declined from 21 per cent., on March 10th, to 2 per cent., and the spleen decreased considerably in size. At this time, the patient suddenly failed in strength and died from general asthenia. There had been extensive *x*-ray burns, which, however, were healing nicely and there was no evidence of general toxemia. An autopsy was made and the usual characters of the leukemic organs were recognized.

George Dock[1] has published a complete review of the subject of Röntgen-ray treatment of leukemia, based upon the study of the reports of 29 cases. Several other cases are referred to indirectly in the literature but could not be tabulated. Two cases of acute lymphatic leukemia were treated, and both died, 1 too early after the treatment was begun to have any bearing on the effects of the treatment. The case reported by Capps and Smith died within ten days, and should also, in Dock's opinion, be excluded from serious consideration. There is, however, nothing better to offer. Of chronic lymphatic cases, there were 5, of which that of Senn, reported in April, 1903, was still living in March, 1904, though reported as dead in Capps and Smith's table. In the other chronic lymphatic cases the results were uniformly encouraging, even when the ultimate outcome was a fatal one. There were 21 cases of mixed-celled myologenous or splenomedullary leu-

[1] *American Medicine*, Dec. 24, 1904.

kemia. Some of these cases were treated for too short a time to receive serious consideration. In 11 of the patients, the leukocytes fell to normal or near it. In 7 other cases, the reduction was less marked, the number at the conclusion of the treatment being still such as to suggest leukemia. In a number of the cases marked improvement of a qualitative character occurred, as shown by the disappearance of myelocytes or the reduction in their proportions. The effect of the treatment on the number of red corpuscles was favorable, again occurring in all but 1 of 12 myelogenous cases. Nucleated-red corpuscles often disappeared, and the hemoglobin usually increased with the number of red corpuscles. The effects of the treatment on the spleen and glands was most striking. In all of the chronic cases the glands diminished and sometimes have reached the normal size, and a similar reduction in the size of the spleen was observed.

A complete reduction of the enlarged spleen can not, however, be always expected, as the amount of connective tissue may prevent shrinkage to this point. Dock, however, states that he can not assume with some writers that in no case of leukemia has the spleen reached a normal size under the treatment. In some cases there was marked improvement in the patient's general condition, though the blood-picture was not conspicuously altered.

Technic of Treatment.—Some of the patients were treated only over the spleen; others over the spleen, epiphyses of the bones, or the long bones themselves, and the sternum. None of the cases were treated over the bones alone. Dock states he is making some observations in this direction, though with disappointing results. The length of exposure has been about the same in different cases. Ten to twenty minutes' exposure in one place, or a total exposure of about that duration in different places have been most frequent. The treatments have been given every day, every other day, or at longer intervals. It is impossible to estimate the dosage of the treatment, and the effects on the patient have usually been the factor governing the applications.

Duration of the Treatment.—The length of time in which the leukocytes were reduced to the normal in the favorable cases varied from a month up to six months.

Unfavorable Results.—The treatment has been found dangerous on account of the risk of dermatitis and burns, and probably *also on* account of certain toxic results as yet impossible to explain.

Conclusions.—Dock concludes that under this treatment some cases undergo marked change for the better; in other cases the effects are imperfect or developing. In no case has the treatment been carried

out long enough to speak of a cure. The action of the Röntgen rays is probably upon the tissues that produce the pathologic leukocytes, either directly or through the production or setting free of substances that influence cell formation, degeneration, chemotaxis, or all of these processes.

No stronger claim can be made for this treatment than for arsenic and certain serums or bacterial toxic substances, but it may prove more certain in its action than arsenic, and can be more readily applied in practice than the injection methods. No special directions can be laid down for the treatment, but great care must be taken to avoid burns. —Ed.]

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